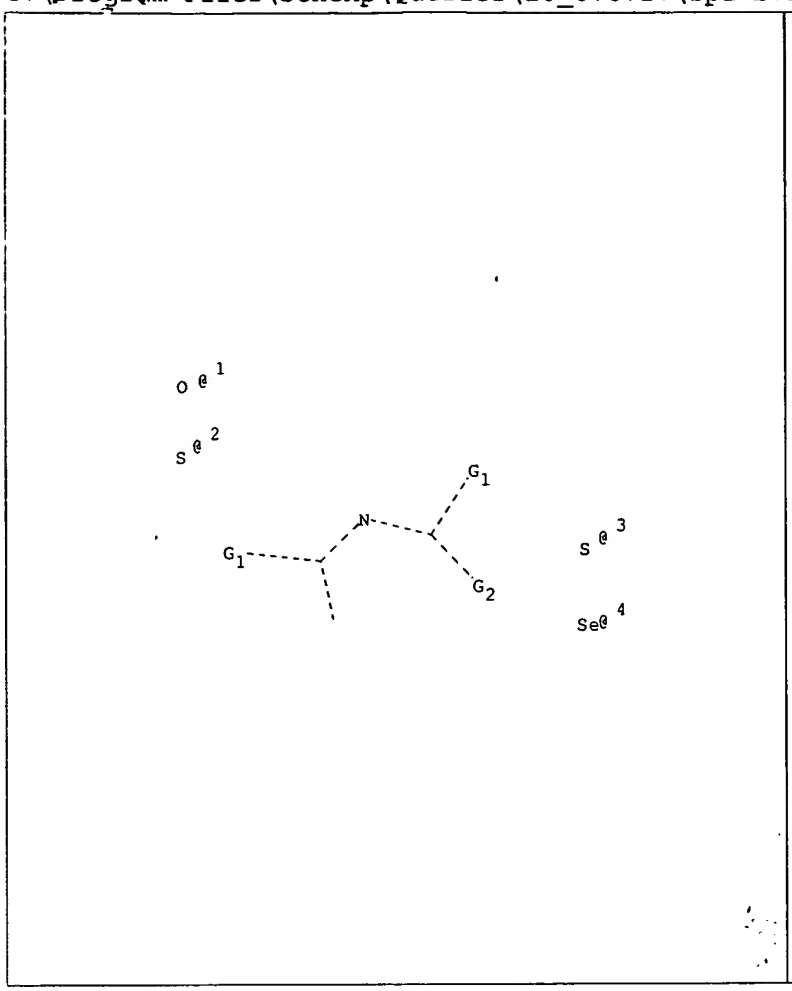
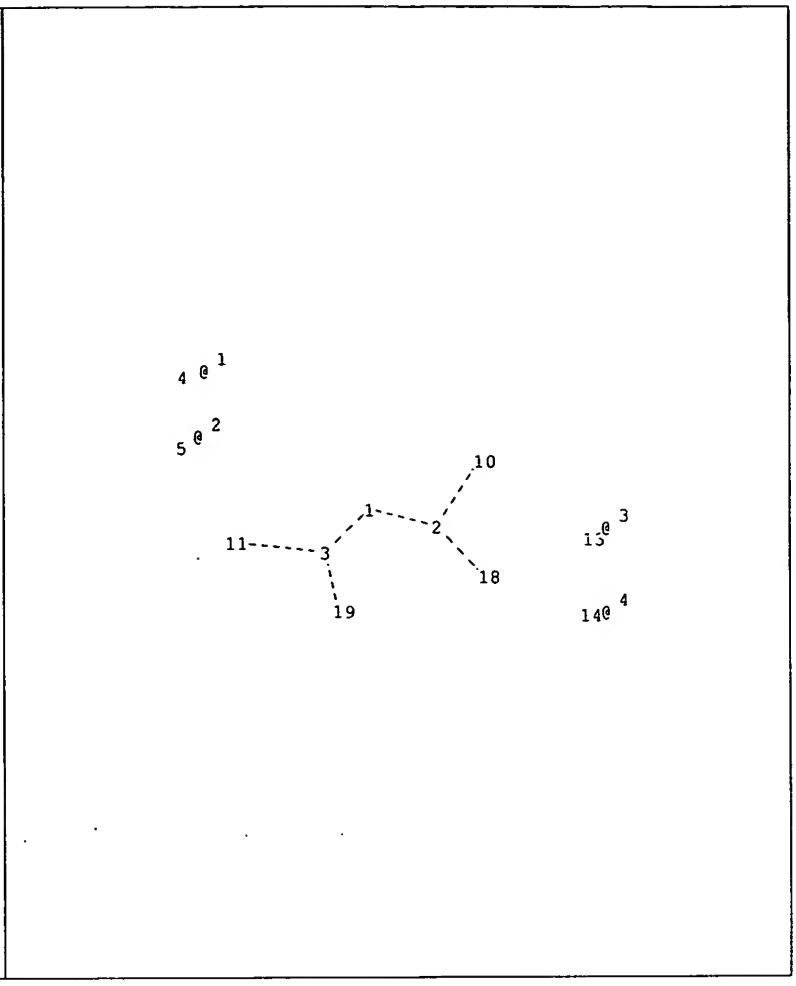
C:\Program Files\Stnexp\Queries\10_676727\spi-b.str

structure "L7"





chain nodes :
    4 5 10 11
ring nodes :
    1 2 3 13 14 18 19
chain bonds :
    2-10 3-11
ring bonds :
    1-2 1-3 2-18 3-19
exact/norm bonds :
    1-2 1-3 2-10 2-18 3-11 3-19

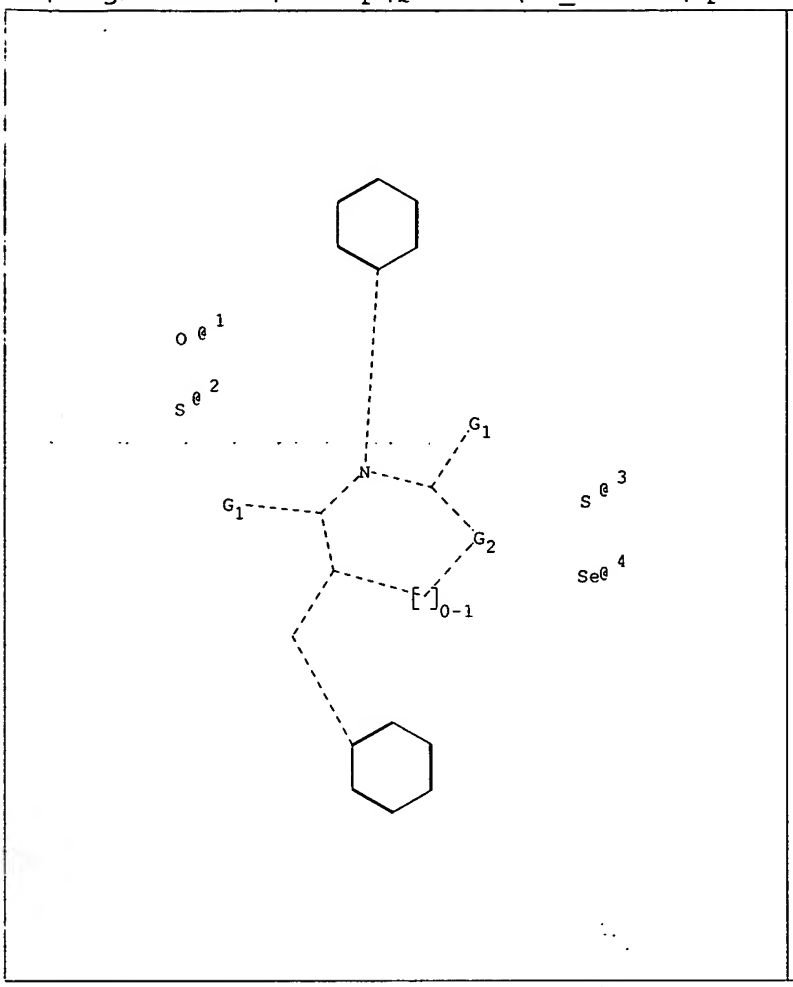
G1:[*1],[*2]

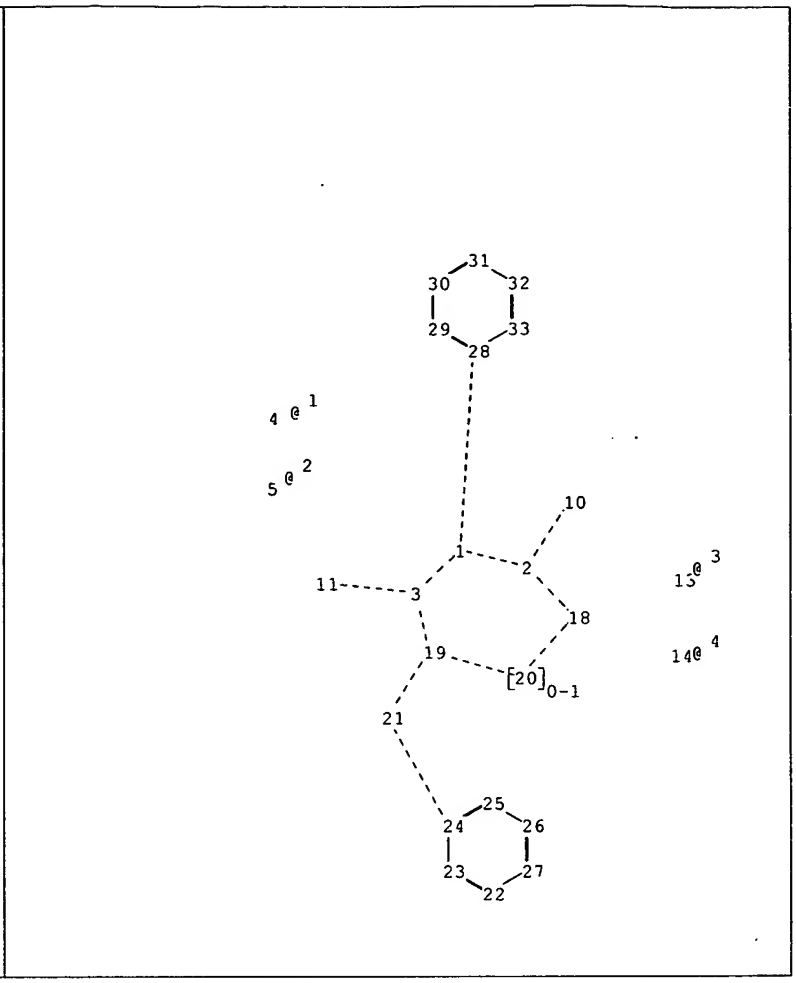
G2:[*3],[*4]

Connectivity :
    2:3 E exact RC ring/chain 3:3 E exact RC ring/chain 4:1 E exact RC ring/chain
    5:1 E exact RC ring/chain
Match level :
    1:Atom 2:Atom 3:Atom 4:CLASS 5:CLASS 10:CLASS 11:CLASS 13:Atom 14:Atom 18:CLASS
    19:Atom

C:\Program Files\Stnexp\Queries\10_676727\spic.str

structure "L56"





chain nodes :
4 5 10 11 21
ring nodes :
1 2 3 13 14 18 19 20 22 23 24 25 26 27 28 29 30 31 32 33
chain bonds :
1-28 2-10 3-11 19-21 21-24
ring bonds :
1-2 1-3 2-18 3-19 18-20 19-20 22-23 22-27 23-24 24-25 25-26 26-27 28-29
28-33 29-30 30-31 31-32 32-33
exact/norm bonds :
1-2 1-3 1-28 2-10 2-18 3-11 3-19 18-20 19-20 19-21 21-24
normalized bonds :
22-23 22-27 23-24 24-25 25-26 26-27 28-29 28-33 29-30 30-31 31-32 32-33

G1:[*1],[*2]

G2:[*3],[*4]

Connectivity :
2:3 E exact RC ring/chain 3:3 E exact RC ring/chain 4:1 E exact RC ring/chain
5:1 E exact RC ring/chain
Match level :
1:Atom 2:Atom 3:Atom 4:CLASS 5:CLASS 10:CLASS 11:CLASS 13:Atom 14:Atom 18:CLASS
19:Atom 20:Atom 21:CLASS 22:Atom 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom
29:Atom 30:Atom 31:Atom 32:Atom 33:Atom

Search history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=> d his full

     (FILE 'HOME' ENTERED AT 09:00:18 ON 16 FEB 2006)

     FILE 'REGISTRY' ENTERED AT 09:00:36 ON 16 FEB 2006
L1      1109869 SEA ABB=ON  PLU=ON  NCSC2/ESS
L2       985269 SEA ABB=ON  PLU=ON  L1 AND O>0

     FILE 'CAPLUS' ENTERED AT 09:02:06 ON 16 FEB 2006
               E US2003-676727/APPS
L3             1 SEA ABB=ON  PLU=ON  US2003-676727/AP
               D SCA
               SEL RN
               D IALL

     FILE 'REGISTRY' ENTERED AT 09:04:13 ON 16 FEB 2006
L4            13 SEA ABB=ON  PLU=ON  (121-44-8/BI OR 292174-08-4/BI OR 301308-44
               -1/BI OR 303056-54-4/BI OR 307510-92-5/BI OR 328250-71-1/BI OR
               504-78-9/BI OR 50718-91-7/BI OR 535962-72-2/BI OR 619-66-9/BI
               OR 677027-74-6/BI OR 677027-75-7/BI OR 98-16-8/BI)
               D SCA

     FILE 'STNGUIDE' ENTERED AT 09:05:35 ON 16 FEB 2006

     FILE 'STNGUIDE' ENTERED AT 09:26:02 ON 16 FEB 2006

     FILE 'REGISTRY' ENTERED AT 09:54:31 ON 16 FEB 2006
L*** DEL           STRUCTURE UPLOADED
L*** DEL         0 S L*** SAM SSS
L7               STRUCTURE UPLOADED
L8            50 SEA SSS SAM L7
               D STAT QUE L8
L*** DEL         0 S L4 AND L8
L9        101796 SEA SSS FUL L7

     FILE 'CAPLUS' ENTERED AT 09:59:24 ON 16 FEB 2006
L10        11681 SEA ABB=ON  PLU=ON  L9

     FILE 'REGISTRY' ENTERED AT 09:59:48 ON 16 FEB 2006
               SAVE TEMP L9 SPI727STRB/A

     FILE 'CAPLUS' ENTERED AT 10:00:29 ON 16 FEB 2006

     FILE 'STNGUIDE' ENTERED AT 10:00:42 ON 16 FEB 2006

     FILE 'CAPLUS' ENTERED AT 10:08:23 ON 16 FEB 2006
L11        10928 SEA ABB=ON  PLU=ON  CYSTIC?/OBI
L12        20440 SEA ABB=ON  PLU=ON  ?CYSTIC?/BI
L13           23 SEA ABB=ON  PLU=ON  L11 AND L10
               E CFTR+ALL/CT
               E E2+ALL
L14         4392 SEA ABB=ON  PLU=ON  CFTR?/BI
L15           13 SEA ABB=ON  PLU=ON  L14 AND L10
L*** DEL         0 S L15 NOT L13
L16          162 SEA ABB=ON  PLU=ON  L12 AND L10
L17          139 SEA ABB=ON  PLU=ON  L16 NOT L13

     FILE 'STNGUIDE' ENTERED AT 10:18:11 ON 16 FEB 2006

     FILE 'CAPLUS' ENTERED AT 10:49:51 ON 16 FEB 2006
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                E CYSTIC FIBROSIS+ALL/CT
L18          504 SEA ABB=ON  PLU=ON  ?FIBROCYSTIC?/BI
L19            1 SEA ABB=ON  PLU=ON  (?FIBRO CYSTIC?)/BI
                D SCA
L20        11128 SEA ABB=ON  PLU=ON  (?CYSTIC FIBRO?)/BI
L21        11128 SEA ABB=ON  PLU=ON  (L19 OR L20)
L22           23 SEA ABB=ON  PLU=ON  L21 AND L10
L*** DEL       0 S L22 NOT L13
L23        10507 SEA ABB=ON  PLU=ON  ION TRANSPORT/OBI
L24            2 SEA ABB=ON  PLU=ON  L10 AND L23
                D SCA
L25        62389 SEA ABB=ON  PLU=ON  ((ION? OR CHLOR?) (3A) ?TRANSP?)/BI
L26           28 SEA ABB=ON  PLU=ON  L10 AND L25
L27           19 SEA ABB=ON  PLU=ON  L26 NOT (L13 OR L15 OR L22 OR L24)
                D SCA
L28          379 SEA ABB=ON  PLU=ON  VERKMAN A?/AU
L29         1877 SEA ABB=ON  PLU=ON  MA T?/AU
L30           60 SEA ABB=ON  PLU=ON  L28 AND L29
                E MA T/AU
L31            3 SEA ABB=ON  PLU=ON  L30 AND L10
L32            8 SEA ABB=ON  PLU=ON  L30 AND (L11 OR L12 OR L14 OR L18 OR L19
                OR L20 OR L23 OR L25)

     FILE 'REGISTRY' ENTERED AT 11:12:53 ON 16 FEB 2006
                D SCA L4
                E  "BENZOIC ACID, 4-((4-OXO-2-THIOXO-3-(3-(TRIFLUOROMETHYL)PHEN
L33            1 SEA ABB=ON  PLU=ON  "BENZOIC ACID, 4-((4-OXO-2-THIOXO-3-(3-(TRI
                FLUOROMETHYL)PHENYL)-5-THIAZOLIDINYLIDENE)METHYL)-"/CN

     FILE 'CAPLUS' ENTERED AT 11:18:22 ON 16 FEB 2006
L34            9 SEA ABB=ON  PLU=ON  L33

     FILE 'REGISTRY' ENTERED AT 11:19:03 ON 16 FEB 2006

     FILE 'REGISTRY' ENTERED AT 11:19:09 ON 16 FEB 2006
L35              STR 307510-92-5
L36            0 SEA FAM SAM L35
L37            0 SEA SUB=L9 FAM SAM L35
L38            2 SEA SUB=L9 FAM FUL L35
                D SCA

     FILE 'CAPLUS' ENTERED AT 11:20:47 ON 16 FEB 2006
L39            9 SEA ABB=ON  PLU=ON  L38
L40            9 SEA ABB=ON  PLU=ON  L39 AND (L11 OR L12 OR L14 OR (L18 OR L19
                OR L20) OR L23)
L41         4349 SEA ABB=ON  PLU=ON  L9 (L) (THU OR PAC OR DMA OR PKT OR
                BAC)/RL
L42           19 SEA ABB=ON  PLU=ON  L41 AND L25
L43           14 SEA ABB=ON  PLU=ON  L42 NOT (L13 OR L15 OR L22 OR L24)

     FILE 'MEDLINE' ENTERED AT 11:28:17 ON 16 FEB 2006
L44        25743 SEA ABB=ON  PLU=ON  CYSTIC FIBR?
L45         3738 SEA ABB=ON  PLU=ON  CFTR
L46         3396 SEA ABB=ON  PLU=ON  FIBROCYST? OR (FIBRO CYST?)
L47         3752 SEA ABB=ON  PLU=ON  CFTR?
L48          383 SEA ABB=ON  PLU=ON  VERKMAN A?/AU
L49          489 SEA ABB=ON  PLU=ON  MA T?/AU
L50           56 SEA ABB=ON  PLU=ON  L48 AND L49
L51            6 SEA ABB=ON  PLU=ON  L50 AND (L44 OR L45 OR L46 OR L47)
L52           58 SEA ABB=ON  PLU=ON  (L48 OR L49) AND (L44 OR L45 OR L46 OR
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              L47)

     FILE 'STNGUIDE' ENTERED AT 11:34:47 ON 16 FEB 2006

     FILE 'MEDLINE' ENTERED AT 11:44:37 ON 16 FEB 2006
L53            0 SEA ABB=ON  PLU=ON  L38

     FILE 'REGISTRY' ENTERED AT 11:44:50 ON 16 FEB 2006
                SET SMARTSELECT ON
L54             SEL PLU=ON  L38 1- CHEM :       4 TERMS
                SET SMARTSELECT OFF

     FILE 'MEDLINE' ENTERED AT 11:44:51 ON 16 FEB 2006
L55            1 SEA ABB=ON  PLU=ON  L54

     FILE 'STNGUIDE' ENTERED AT 11:49:47 ON 16 FEB 2006

     FILE 'REGISTRY' ENTERED AT 11:49:48 ON 16 FEB 2006
L56             STRUCTURE UPLOADED
L57           50 SEA SUB=L9 SSS SAM L56
L58         7067 SEA SUB=L9 SSS FUL L56
                SAVE TEMP SPI727STRC/A L58

     FILE 'CAPLUS' ENTERED AT 11:51:48 ON 16 FEB 2006
L59          238 SEA ABB=ON  PLU=ON  L58

     FILE 'MEDLINE' ENTERED AT 11:52:14 ON 16 FEB 2006

     FILE 'REGISTRY' ENTERED AT 11:53:49 ON 16 FEB 2006

     FILE 'MEDLINE' ENTERED AT 11:54:33 ON 16 FEB 2006

     FILE 'REGISTRY' ENTERED AT 11:54:43 ON 16 FEB 2006
L60            0 SEA ABB=ON  PLU=ON  L58 AND MEDLINE/LC
L61           29 SEA ABB=ON  PLU=ON  L9 AND MEDLINE/LC

     FILE 'MEDLINE' ENTERED AT 11:56:10 ON 16 FEB 2006
L62         3293 SEA ABB=ON  PLU=ON  L61
L63            1 SEA ABB=ON  PLU=ON  L62 AND (L44 OR L45 OR L46 OR L47)
L64        14298 SEA ABB=ON  PLU=ON  ION? (3A) ?TRANSP?
L65            5 SEA ABB=ON  PLU=ON  L62 AND L64
                D TRIAL 1-5

     FILE 'CAPLUS' ENTERED AT 11:59:17 ON 16 FEB 2006
L66            6 SEA ABB=ON  PLU=ON  L25 AND L59

     FILE 'MEDLINE' ENTERED AT 12:01:13 ON 16 FEB 2006

     FILE 'REGISTRY' ENTERED AT 12:01:27 ON 16 FEB 2006
                SET SMARTSELECT ON
L67             SEL PLU=ON  L61 1- CHEM :     132 TERMS
                SET SMARTSELECT OFF

     FILE 'MEDLINE' ENTERED AT 12:01:32 ON 16 FEB 2006
L68         6472 SEA ABB=ON  PLU=ON  L67
L69           16 SEA ABB=ON  PLU=ON  L68 AND (L44 OR L45 OR L46 OR L47)
                D SCA
                D TRIAL L69 1-16

     FILE 'EMBASE' ENTERED AT 12:04:13 ON 16 FEB 2006
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L70         360 SEA ABB=ON  PLU=ON  VERKMAN A?/AU
L71         405 SEA ABB=ON  PLU=ON  MA T?/AU
L72          56 SEA ABB=ON  PLU=ON  L70 AND L71
L73       53696 SEA ABB=ON  PLU=ON  CYSTIC?
L74        1353 SEA ABB=ON  PLU=ON  (FIBROCYSTIC? OR (FIBRO CYST?))
                E CYSTIC FIBROSIS+ALL/CT
L75           6 SEA ABB=ON  PLU=ON  MUCOVISCOID?
                E CFTR/CT
L76        3377 SEA ABB=ON  PLU=ON  CFTR?
L77           6 SEA ABB=ON  PLU=ON  L70 AND L71 AND (L73 OR L74 OR L75 OR L76)


     FILE 'REGISTRY' ENTERED AT 12:07:32 ON 16 FEB 2006
L78          22 SEA ABB=ON  PLU=ON  L9 AND EMBASE/LC

     FILE 'EMBASE' ENTERED AT 12:07:43 ON 16 FEB 2006

     FILE 'REGISTRY' ENTERED AT 12:08:06 ON 16 FEB 2006
                SET SMARTSELECT ON
L79             SEL PLU=ON  L78 1- CHEM :     110 TERMS
                SET SMARTSELECT OFF

     FILE 'EMBASE' ENTERED AT 12:08:08 ON 16 FEB 2006
L80         8516 SEA ABB=ON  PLU=ON  L79
L81         8516 SEA ABB=ON  PLU=ON  (L78 OR L80 )

     FILE 'REGISTRY' ENTERED AT 12:08:59 ON 16 FEB 2006
                SET SMARTSELECT ON
L82             SEL PLU=ON  L38 1- CHEM :       4 TERMS
                SET SMARTSELECT OFF

     FILE 'EMBASE' ENTERED AT 12:09:00 ON 16 FEB 2006
L83             2 SEA ABB=ON  PLU=ON  L82
L84             2 SEA ABB=ON  PLU=ON  (L38 OR L83 )
L85             2 SEA ABB=ON  PLU=ON  L84 AND ((L73 OR L74 OR L75 OR L76))
L86            32 SEA ABB=ON  PLU=ON  L81 AND (L73 OR L74 OR L75 OR L76)
                D SCA
                D TRIAL 1-5
L87             1 SEA ABB=ON  PLU=ON  L77 AND L81

     FILE 'MEDLINE' ENTERED AT 12:14:55 ON 16 FEB 2006
L88             8 SEA ABB=ON  PLU=ON  (L48 OR L49) AND L68

     FILE 'EMBASE' ENTERED AT 12:16:50 ON 16 FEB 2006
L89             5 SEA ABB=ON  PLU=ON  (L70 OR L71) AND L80

     FILE 'CAPLUS' ENTERED AT 12:17:20 ON 16 FEB 2006
L90             8 SEA ABB=ON  PLU=ON  L10 AND (L28 OR L29)

     FILE 'BIOSIS' ENTERED AT 12:17:51 ON 16 FEB 2006
L91           673 SEA ABB=ON  PLU=ON  VERKMAN A?/AU
L92           726 SEA ABB=ON  PLU=ON  MA T?/AU
L93           113 SEA ABB=ON  PLU=ON  L91 AND L92

     FILE 'REGISTRY' ENTERED AT 12:18:18 ON 16 FEB 2006
L94            52 SEA ABB=ON  PLU=ON  L9 AND BIOSIS/LC

     FILE 'BIOSIS' ENTERED AT 12:18:35 ON 16 FEB 2006
L95          4798 SEA ABB=ON  PLU=ON  L94
L96         47945 SEA ABB=ON  PLU=ON  CYSTIC?
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L97         1202 SEA ABB=ON  PLU=ON  FIBROCYST? OR (FIBRO CYST?)
L98         4750 SEA ABB=ON  PLU=ON  CFTR
L99         4793 SEA ABB=ON  PLU=ON  CFTR?
L100           1 SEA ABB=ON  PLU=ON  L95 AND (L96 OR L97 OR L98 OR L99)
L101           1 SEA ABB=ON  PLU=ON  (L91 OR L92) AND L95
L102          60 SEA ABB=ON  PLU=ON  (L91 OR L92) AND (L96 OR L97 OR L98 OR
                 L99)
L103           6 SEA ABB=ON  PLU=ON  L91 AND L92 AND (L96 OR L97 OR L98 OR L99)


     FILE 'REGISTRY' ENTERED AT 12:21:17 ON 16 FEB 2006
                 SET SMARTSELECT ON
L104             SEL PLU=ON  L94 1- CHEM :     237 TERMS
                 SET SMARTSELECT OFF

     FILE 'BIOSIS' ENTERED AT 12:21:23 ON 16 FEB 2006
L105        6185 SEA ABB=ON  PLU=ON  L104
L106           6 SEA ABB=ON  PLU=ON  L105 AND (L96 OR L97 OR L98 OR L99)
L107           1 SEA ABB=ON  PLU=ON  L105 AND L93

     FILE 'REGISTRY' ENTERED AT 12:23:14 ON 16 FEB 2006
                 SET SMARTSELECT ON
L108             SEL PLU=ON  L38 1- CHEM :       4 TERMS
                 SET SMARTSELECT OFF

     FILE 'BIOSIS' ENTERED AT 12:23:15 ON 16 FEB 2006
L109           2 SEA ABB=ON  PLU=ON  L108
L110           2 SEA ABB=ON  PLU=ON  (L38 OR L109 )

     FILE 'REGISTRY' ENTERED AT 12:24:16 ON 16 FEB 2006
L111             ANALYZE PLU=ON  L38 1- LC :       5 TERMS
                 D

     FILE 'USPATFULL' ENTERED AT 12:25:09 ON 16 FEB 2006
L112           2 SEA ABB=ON  PLU=ON  L38

     FILE 'REGISTRY' ENTERED AT 12:25:56 ON 16 FEB 2006
L113       11556 SEA ABB=ON  PLU=ON  L9 AND USPATFULL/LC

     FILE 'USPATFULL' ENTERED AT 12:26:20 ON 16 FEB 2006

     FILE 'REGISTRY' ENTERED AT 12:26:53 ON 16 FEB 2006
L114          45 SEA ABB=ON  PLU=ON  L58 AND USPATFULL/LC

     FILE 'USPATFULL' ENTERED AT 12:27:07 ON 16 FEB 2006
L115          23 SEA ABB=ON  PLU=ON  L114
L116       11441 SEA ABB=ON  PLU=ON  CYSTIC FIBR?
L117        1108 SEA ABB=ON  PLU=ON  FIBROCYSTIC? OR (FIBRO CYSTIC?)
L118        3284 SEA ABB=ON  PLU=ON  CFTR?
L119           4 SEA ABB=ON  PLU=ON  L115 AND ((L116 OR L117 OR L118))

     FILE 'REGISTRY' ENTERED AT 12:29:19 ON 16 FEB 2006
                 SET SMARTSELECT ON
L120             SEL PLU=ON  L38 1- CHEM :       4 TERMS
                 SET SMARTSELECT OFF

     FILE 'USPATFULL' ENTERED AT 12:29:20 ON 16 FEB 2006
L121           3 SEA ABB=ON  PLU=ON  L120
L122           3 SEA ABB=ON  PLU=ON  (L112 OR L121) AND (L116 OR L117 OR L118)
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     FILE 'REGISTRY' ENTERED AT 12:30:05 ON 16 FEB 2006
                SET SMARTSELECT ON
L123            SEL PLU=ON  L114 1- CHEM :      59 TERMS
                SET SMARTSELECT OFF

     FILE 'USPATFULL' ENTERED AT 12:30:10 ON 16 FEB 2006
L124          4 SEA ABB=ON  PLU=ON  L123
L125          4 SEA ABB=ON  PLU=ON  L124 AND (L116 OR L117 OR L118)
L126          4 SEA ABB=ON  PLU=ON  VERKMAN A?/AU
L127        100 SEA ABB=ON  PLU=ON  MA T?/AU
L128          2 SEA ABB=ON  PLU=ON  L126 AND L127
L129          4 SEA ABB=ON  PLU=ON  (L126 OR L127) AND (L116 OR L117 OR L118)
L130          2 SEA ABB=ON  PLU=ON  (L126 OR L127) AND (L119 OR L125 OR L122)

     FILE 'STNGUIDE' ENTERED AT 12:33:03 ON 16 FEB 2006

     FILE 'REGISTRY' ENTERED AT 12:34:11 ON 16 FEB 2006
                D STAT QUE L9
                D STAT QUE L38
                D STAT QUE L58

     FILE 'STNGUIDE' ENTERED AT 12:35:04 ON 16 FEB 2006

     FILE 'CAPLUS' ENTERED AT 12:38:56 ON 16 FEB 2006
                D QUE NOS L31
                D QUE NOS L32
                D QUE NOS L90
L131         13 SEA ABB=ON  PLU=ON  L31 OR L32 OR L90

     FILE 'MEDLINE' ENTERED AT 12:38:59 ON 16 FEB 2006
                D QUE NOS L51
                D QUE NOS L88
L132         13 SEA ABB=ON  PLU=ON  L51 OR L88

     FILE 'EMBASE' ENTERED AT 12:39:03 ON 16 FEB 2006
                D QUE NOS L77
                D QUE NOS L87
                D QUE NOS L89
L133         10 SEA ABB=ON  PLU=ON  L77 OR L87 OR L89

     FILE 'BIOSIS' ENTERED AT 12:39:07 ON 16 FEB 2006
                D QUE NOS L101
                D QUE NOS L103
                D QUE NOS L107
L134          6 SEA ABB=ON  PLU=ON  L101 OR L103 OR L107

     FILE 'USPATFULL' ENTERED AT 12:39:11 ON 16 FEB 2006
                D QUE NOS L128
                D QUE NOS L129
                D QUE NOS L130
L135          4 SEA ABB=ON  PLU=ON  (L128 OR L129 OR L130)

     FILE 'STNGUIDE' ENTERED AT 12:39:26 ON 16 FEB 2006

     FILE 'CAPLUS, MEDLINE, EMBASE, BIOSIS, USPATFULL' ENTERED AT 12:40:30 ON
     16 FEB 2006
L136         23 DUP REM L131 L132 L133 L134 L135 (23 DUPLICATES REMOVED)
                       ANSWERS '1-13' FROM FILE CAPLUS
                       ANSWERS '14-18' FROM FILE MEDLINE
                       ANSWERS '19-20' FROM FILE EMBASE
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                    ANSWERS '21-23' FROM FILE USPATFULL
                D IBIB ABS HITIND HITSTR L136 1-13
                D IALL L136 14-20
                D IBIB ABS HITSTR L136 21-23

     FILE 'STNGUIDE' ENTERED AT 12:42:24 ON 16 FEB 2006

     FILE 'CAPLUS' ENTERED AT 12:45:36 ON 16 FEB 2006
                D QUE NOS L39
                D QUE NOS L40
L137          3 SEA ABB=ON  PLU=ON  ((L39 OR L40)) NOT L131

     FILE 'MEDLINE' ENTERED AT 12:45:39 ON 16 FEB 2006
                D QUE NOS L55
L138          0 SEA ABB=ON  PLU=ON  L55 NOT L132

     FILE 'EMBASE' ENTERED AT 12:45:42 ON 16 FEB 2006
                D QUE NOS L85
L139          1 SEA ABB=ON  PLU=ON  L85 NOT L133

     FILE 'BIOSIS' ENTERED AT 12:45:45 ON 16 FEB 2006
                D QUE NOS L110
L140          2 SEA ABB=ON  PLU=ON  L110 NOT L134

     FILE 'USPATFULL' ENTERED AT 12:45:47 ON 16 FEB 2006
                D QUE NOS L122
L141          1 SEA ABB=ON  PLU=ON  L122 NOT L135

     FILE 'STNGUIDE' ENTERED AT 12:46:00 ON 16 FEB 2006

     FILE 'CAPLUS, EMBASE, BIOSIS, USPATFULL' ENTERED AT 12:47:01 ON 16 FEB
     2006
L142          5 DUP REM L137 L139 L140 L141 (2 DUPLICATES REMOVED)
                      ANSWERS '1-3' FROM FILE CAPLUS
                      ANSWER '4' FROM FILE BIOSIS
                      ANSWER '5' FROM FILE USPATFULL
                D IBIB ABS HITIND HITSTR L142 1-3
                D IALL L142 4
                D IBIB ABS KWIC HITSTR L142 5

     FILE 'STNGUIDE' ENTERED AT 12:48:41 ON 16 FEB 2006

     FILE 'CAPLUS' ENTERED AT 12:54:29 ON 16 FEB 2006
                D QUE NOS L13
                D QUE NOS L15
                D QUE NOS L22
                D QUE NOS L24
                D QUE NOS L66
L143         15 SEA ABB=ON  PLU=ON  (L13 OR L15 OR L22 OR L24 OR L66) NOT
                (L137 OR L131)

     FILE 'MEDLINE' ENTERED AT 12:54:34 ON 16 FEB 2006
                D QUE NOS L60
                D QUE NOS L65
                D QUE NOS L69
L144         15 SEA ABB=ON  PLU=ON  (L60 OR L65 OR L69) NOT (L132 OR L138)

     FILE 'EMBASE' ENTERED AT 12:54:38 ON 16 FEB 2006
                D QUE NOS L86
L145         26 SEA ABB=ON  PLU=ON  L86 NOT (L133 OR L139)
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     FILE 'BIOSIS' ENTERED AT 12:54:41 ON 16 FEB 2006
               D QUE NOS L100
               D QUE NOS L106
L146           3 SEA ABB=ON  PLU=ON  (L100 OR L106) NOT (L134 OR L140)

     FILE 'USPATFULL' ENTERED AT 12:54:44 ON 16 FEB 2006
               D QUE NOS L119
               D QUE NOS L125
L147           2 SEA ABB=ON  PLU=ON  (L119 OR L125) NOT (L141 OR L135)

     FILE 'STNGUIDE' ENTERED AT 12:54:55 ON 16 FEB 2006

     FILE 'CAPLUS, MEDLINE, EMBASE, BIOSIS, USPATFULL' ENTERED AT 12:56:13 ON
     16 FEB 2006
L148          56 DUP REM L143 L144 L145 L146 L147 (5 DUPLICATES REMOVED)
                    ANSWERS '1-15' FROM FILE CAPLUS
                    ANSWERS '16-29' FROM FILE MEDLINE
                    ANSWERS '30-53' FROM FILE EMBASE
                    ANSWER '54' FROM FILE BIOSIS
                    ANSWERS '55-56' FROM FILE USPATFULL
               D IBIB ABS HITIND HITSTR L148 1-15
               D IALL L148 16-54
               D IBIB ABS KWIC HITSTR L148 55-56

     FILE HOME

     FILE REGISTRY
     Property values tagged with IC are from the ZIC/VINITI data file
     provided by InfoChem.

     STRUCTURE FILE UPDATES:   14 FEB 2006  HIGHEST RN 874270-88-9
     DICTIONARY FILE UPDATES:  14 FEB 2006  HIGHEST RN 874270-88-9

     New CAS Information Use Policies, enter HELP USAGETERMS for details.

     TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

       Please note that search-term pricing does apply when
       conducting SmartSELECT searches.

     ************************************************************
     *                                                          *
     * The CA roles and document type information have been removed from *
     * the IDE default display format and the ED field has been added,   *
     * effective March 20, 2005.  A new display format, IDERL, is now    *
     * available and contains the CA role and document type information. *
     *                                                          *
     ************************************************************

     Structure search iteration limits have been increased.  See HELP SLIMITS
     for details.

     REGISTRY includes numerically searchable data for experimental and
     predicted properties as well as tags indicating availability of
     experimental property data in the original document.  For information
     on property searching in REGISTRY, refer to:

     http://www.cas.org/ONLINE/UG/regprops.html
```

FILE CAPLUS

FILE COVERS 1907 - 16 Feb 2006 VOL 144 ISS 8
FILE LAST UPDATED: 15 Feb 2006 (20060215/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

http://www.cas.org/infopolicy.html

FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Feb 10, 2006 (20060210/UP).

FILE MEDLINE
FILE LAST UPDATED: 15 FEB 2006 (20060215/UP). FILE COVERS 1950 TO DATE.

On December 11, 2005, the 2006 MeSH terms were loaded.

The MEDLINE reload for 2006 will soon be available. For details on the 2005 reload, enter HELP RLOAD at an arrow promt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate

FILE EMBASE
FILE COVERS 1974 TO 9 Feb 2006 (20060209/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE BIOSIS
FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 15 February 2006 (20060215/ED)

FILE USPATFULL
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 16 Feb 2006 (20060216/PD)
FILE LAST UPDATED: 16 Feb 2006 (20060216/ED)
HIGHEST GRANTED PATENT NUMBER: US7000250
HIGHEST APPLICATION PUBLICATION NUMBER: US2006037120
CA INDEXING IS CURRENT THROUGH 14 Feb 2006 (20060214/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 16 Feb 2006 (20060216/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2005

=>

doses) in mice over the first 6 wk of life. The metabolic stability, enterohepatic recirculation, slow renal elimination, and intestinal accumulation of CFTRinh-172 account for its efficacy as an antidiarrheal.

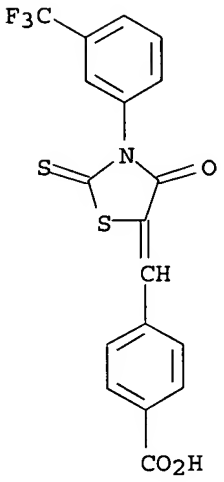
CC 1-9 (Pharmacology)

IT **307510-92-5**
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vivo pharmacol. and antidiarrheal efficacy of a thiazolidinone CFTR inhibitor in rodents)

IT **307510-92-5**
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vivo pharmacol. and antidiarrheal efficacy of a thiazolidinone CFTR inhibitor in rodents)

RN 307510-92-5 CAPLUS

CN Benzoic acid, 4-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinylidene]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 2 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2004:269861 CAPLUS

DOCUMENT NUMBER: 140:247127

TITLE: Thiazolidinone compound **cystic fibrosis** transmembrane conductance regulator protein inhibitors, uses, and animal model of **CFTR**-mediated disease

INVENTOR(S): **Verkman, Alan; Ma, Tonghui**

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 22 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004063695	A1	20040401	US 2002-262573	20020930

FILE 'MEDLINE' ENTERED AT 12:40:30 ON 16 FEB 2006

FILE 'EMBASE' ENTERED AT 12:40:30 ON 16 FEB 2006

FILE 'BIOSIS' ENTERED AT 12:40:30 ON 16 FEB 2006

FILE 'USPATFULL' ENTERED AT 12:40:30 ON 16 FEB 2006

PROCESSING COMPLETED FOR L131
PROCESSING COMPLETED FOR L132
PROCESSING COMPLETED FOR L133
PROCESSING COMPLETED FOR L134
PROCESSING COMPLETED FOR L135
L136 23 DUP REM L131 L132 L133 L134 L135 (23 DUPLICATES REMOVED)
ANSWERS '1-13' FROM FILE CAPLUS
ANSWERS '14-18' FROM FILE MEDLINE
ANSWERS '19-20' FROM FILE EMBASE
ANSWERS '21-23' FROM FILE USPATFULL

=> d ibib abs hitind hitstr L136 1-13; d iall L136 14-20; d ibib abs hitstr L136 21-23

L136 ANSWER 1 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2005:37884 CAPLUS
DOCUMENT NUMBER: 142:403893
TITLE: In vivo pharmacology and antidiarrheal efficacy of a thiazolidinone CFTR inhibitor in rodents
AUTHOR(S): Sonawane, N. D.; Muanprasat, Chatchai; Nagatani, Ray, Jr.; Song, Yuanlin; **Verkman, A. S.**
CORPORATE SOURCE: Departments of Medicine and Physiology, Cardiovascular Research Institute, University of California, San Francisco, CA, 94143-0521, USA
SOURCE: Journal of Pharmaceutical Sciences (2005), 94(1), 134-143
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A small-mol. inhibitor of the cystic fibrosis transmembrane conductance regulator (CFTR), 3-[(3-trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone (CFTRinh-172), reduces enterotoxin-induced intestinal fluid secretion in rodents. Here, we study CFTRinh-172 pharmacol. and antidiarrheal efficacy in rodents using 14C-labeled CFTRinh-172, liquid chromatog./mass spectrometry, and a closed intestinal loop model of fluid secretion. CFTRinh-172 was cleared primarily by renal glomerular filtration without chemical modification. CFTRinh-172 accumulated in liver within 5 min after i.v. infusion in mice, and was concentrated fivefold in bile over blood. At 30-240 min, CFTRinh-172 was found mainly in liver, intestine, and kidney, with little detectable in the brain, heart, skeletal muscle, or lung. Pharmacokinetic anal. in rats following i.v. bolus infusion showed a distribution volume of 770 mL with redistribution and elimination half-times of 0.14 h and 10.3 h, resp. CFTRinh-172 was stable in hepatic microsomes. Closed-loop studies in mice indicated that a single i.p. injection of 20 μg CFTRinh-172 inhibited fluid accumulation at 6 h after cholera toxin by >90% in duodenum and jejunum, .apprx.60% in ileum and <10% in colon. No toxicity was seen after high-dose CFTRinh-172 administration (3 mg/kg/day in two daily

```
=> d que nos L128

L126          4 SEA FILE=USPATFULL ABB=ON  PLU=ON  VERKMAN A?/AU
L127        100 SEA FILE=USPATFULL ABB=ON  PLU=ON  MA T?/AU
L128          2 SEA FILE=USPATFULL ABB=ON  PLU=ON  L126 AND L127


=> d que nos L129

L116      11441 SEA FILE=USPATFULL ABB=ON  PLU=ON  CYSTIC FIBR?
L117       1108 SEA FILE=USPATFULL ABB=ON  PLU=ON  FIBROCYSTIC? OR (FIBRO
                CYSTIC?)
L118       3284 SEA FILE=USPATFULL ABB=ON  PLU=ON  CFTR?
L126          4 SEA FILE=USPATFULL ABB=ON  PLU=ON  VERKMAN A?/AU
L127        100 SEA FILE=USPATFULL ABB=ON  PLU=ON  MA T?/AU
L129          4 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L126 OR L127) AND (L116 OR
                L117 OR L118)


=> d que nos L130

L7              STR
L9       101796 SEA FILE=REGISTRY SSS FUL L7
L35             STR
L38           2 SEA FILE=REGISTRY SUB=L9 FAM FUL L35
L56             STR
L58        7067 SEA FILE=REGISTRY SUB=L9 SSS FUL L56
L112          2 SEA FILE=USPATFULL ABB=ON  PLU=ON  L38
L114         45 SEA FILE=REGISTRY ABB=ON  PLU=ON  L58 AND USPATFULL/LC
L115         23 SEA FILE=USPATFULL ABB=ON  PLU=ON  L114
L116      11441 SEA FILE=USPATFULL ABB=ON  PLU=ON  CYSTIC FIBR?
L117       1108 SEA FILE=USPATFULL ABB=ON  PLU=ON  FIBROCYSTIC? OR (FIBRO
                CYSTIC?)
L118       3284 SEA FILE=USPATFULL ABB=ON  PLU=ON  CFTR?
L119          4 SEA FILE=USPATFULL ABB=ON  PLU=ON  L115 AND ((L116 OR L117 OR
                L118))
L120            SEL  PLU=ON  L38 1- CHEM :        4 TERMS
L121          3 SEA FILE=USPATFULL ABB=ON  PLU=ON  L120
L122          3 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L112 OR L121) AND (L116 OR
                L117 OR L118)
L123            SEL  PLU=ON  L114 1- CHEM :       59 TERMS
L124          4 SEA FILE=USPATFULL ABB=ON  PLU=ON  L123
L125          4 SEA FILE=USPATFULL ABB=ON  PLU=ON  L124 AND (L116 OR L117 OR
                L118)
L126          4 SEA FILE=USPATFULL ABB=ON  PLU=ON  VERKMAN A?/AU
L127        100 SEA FILE=USPATFULL ABB=ON  PLU=ON  MA T?/AU
L130          2 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L126 OR L127) AND (L119 OR
                L125 OR L122)


=> s L128-L130

L135          4 (L128 OR L129 OR L130)

=> => dup rem L131 L132 L133 L134 L135
FILE 'CAPLUS' ENTERED AT 12:40:30 ON 16 FEB 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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```

```
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 15 February 2006 (20060215/ED)


=> d que nos L101

L7              STR
L9         101796 SEA FILE=REGISTRY SSS FUL L7
L91           673 SEA FILE=BIOSIS ABB=ON  PLU=ON  VERKMAN A?/AU
L92           726 SEA FILE=BIOSIS ABB=ON  PLU=ON  MA T?/AU
L94            52 SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND BIOSIS/LC
L95          4798 SEA FILE=BIOSIS ABB=ON  PLU=ON  L94
L101            1 SEA FILE=BIOSIS ABB=ON  PLU=ON  (L91 OR L92) AND L95


=> d que nos L103

L91           673 SEA FILE=BIOSIS ABB=ON  PLU=ON  VERKMAN A?/AU
L92           726 SEA FILE=BIOSIS ABB=ON  PLU=ON  MA T?/AU
L96         47945 SEA FILE=BIOSIS ABB=ON  PLU=ON  CYSTIC?
L97          1202 SEA FILE=BIOSIS ABB=ON  PLU=ON  FIBROCYST? OR (FIBRO CYST?)
L98          4750 SEA FILE=BIOSIS ABB=ON  PLU=ON  CFTR
L99          4793 SEA FILE=BIOSIS ABB=ON  PLU=ON  CFTR?
L103            6 SEA FILE=BIOSIS ABB=ON  PLU=ON  L91 AND L92 AND (L96 OR L97 OR
                  L98 OR L99)


=> d que nos L107

L7              STR
L9         101796 SEA FILE=REGISTRY SSS FUL L7
L91           673 SEA FILE=BIOSIS ABB=ON  PLU=ON  VERKMAN A?/AU
L92           726 SEA FILE=BIOSIS ABB=ON  PLU=ON  MA T?/AU
L93           113 SEA FILE=BIOSIS ABB=ON  PLU=ON  L91 AND L92
L94            52 SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND BIOSIS/LC
L104              SEL  PLU=ON  L94 1- CHEM :      237 TERMS
L105         6185 SEA FILE=BIOSIS ABB=ON  PLU=ON  L104
L107            1 SEA FILE=BIOSIS ABB=ON  PLU=ON  L105 AND L93


=> s L101 or L103 or L107

L134            6 L101 OR L103 OR L107

=> file uspatfull

FILE 'USPATFULL' ENTERED AT 12:39:11 ON 16 FEB 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 16 Feb 2006 (20060216/PD)
FILE LAST UPDATED: 16 Feb 2006 (20060216/ED)
HIGHEST GRANTED PATENT NUMBER: US7000250
HIGHEST APPLICATION PUBLICATION NUMBER: US2006037120
CA INDEXING IS CURRENT THROUGH 14 Feb 2006 (20060214/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 16 Feb 2006 (20060216/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2005
```

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> d que nos L77

L70          360 SEA FILE=EMBASE ABB=ON  PLU=ON  VERKMAN A?/AU
L71          405 SEA FILE=EMBASE ABB=ON  PLU=ON  MA T?/AU
L73        53696 SEA FILE=EMBASE ABB=ON  PLU=ON  CYSTIC?
L74         1353 SEA FILE=EMBASE ABB=ON  PLU=ON  (FIBROCYSTIC? OR (FIBRO
                 CYST?))
L75            6 SEA FILE=EMBASE ABB=ON  PLU=ON  MUCOVISCOID?
L76         3377 SEA FILE=EMBASE ABB=ON  PLU=ON  CFTR?
L77            6 SEA FILE=EMBASE ABB=ON  PLU=ON  L70 AND L71 AND (L73 OR L74 OR
                 L75 OR L76)

=> d que nos L87

L7               STR
L9         101796 SEA FILE=REGISTRY SSS FUL L7
L70           360 SEA FILE=EMBASE ABB=ON  PLU=ON  VERKMAN A?/AU
L71           405 SEA FILE=EMBASE ABB=ON  PLU=ON  MA T?/AU
L73         53696 SEA FILE=EMBASE ABB=ON  PLU=ON  CYSTIC?
L74          1353 SEA FILE=EMBASE ABB=ON  PLU=ON  (FIBROCYSTIC? OR (FIBRO
                  CYST?))
L75             6 SEA FILE=EMBASE ABB=ON  PLU=ON  MUCOVISCOID?
L76          3377 SEA FILE=EMBASE ABB=ON  PLU=ON  CFTR?
L77             6 SEA FILE=EMBASE ABB=ON  PLU=ON  L70 AND L71 AND (L73 OR L74 OR
                  L75 OR L76)
L78            22 SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND EMBASE/LC
L79               SEL  PLU=ON  L78 1- CHEM :      110 TERMS
L80          8516 SEA FILE=EMBASE ABB=ON  PLU=ON  L79
L81          8516 SEA FILE=EMBASE ABB=ON  PLU=ON  (L78 OR L80 )
L87             1 SEA FILE=EMBASE ABB=ON  PLU=ON  L77 AND L81

=> d que nos L89

L7               STR
L9         101796 SEA FILE=REGISTRY SSS FUL L7
L70           360 SEA FILE=EMBASE ABB=ON  PLU=ON  VERKMAN A?/AU
L71           405 SEA FILE=EMBASE ABB=ON  PLU=ON  MA T?/AU
L78            22 SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND EMBASE/LC
L79               SEL  PLU=ON  L78 1- CHEM :      110 TERMS
L80          8516 SEA FILE=EMBASE ABB=ON  PLU=ON  L79
L89             5 SEA FILE=EMBASE ABB=ON  PLU=ON  (L70 OR L71) AND L80

=> s L77 or L87 or L89

L133           10 L77 OR L87 OR L89

=> file biosis

FILE 'BIOSIS' ENTERED AT 12:39:07 ON 16 FEB 2006
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FILE COVERS 1969 TO DATE.
```

```
=> file medline

[redacted] ENTERED AT 12:38:59 ON 16 FEB 2006

 FILE LAST UPDATED: 15 FEB 2006 (20060215/UP).  FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 will soon be available.  For details
 on the 2005 reload, enter HELP RLOAD at an arrow promt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate

=> d que nos L51

L44        25743 SEA FILE=MEDLINE ABB=ON  PLU=ON  CYSTIC FIBR?
L45         3738 SEA FILE=MEDLINE ABB=ON  PLU=ON  CFTR
L46         3396 SEA FILE=MEDLINE ABB=ON  PLU=ON  FIBROCYST? OR (FIBRO CYST?)
L47         3752 SEA FILE=MEDLINE ABB=ON  PLU=ON  CFTR?
L48          383 SEA FILE=MEDLINE ABB=ON  PLU=ON  VERKMAN A?/AU
L49          489 SEA FILE=MEDLINE ABB=ON  PLU=ON  MA T?/AU
L50           56 SEA FILE=MEDLINE ABB=ON  PLU=ON  L48 AND L49
L51            6 SEA FILE=MEDLINE ABB=ON  PLU=ON  L50 AND (L44 OR L45 OR L46 OR
                 L47)

=> d que nos L88

L7                STR
L9         101796 SEA FILE=REGISTRY SSS FUL L7
L48           383 SEA FILE=MEDLINE ABB=ON  PLU=ON  VERKMAN A?/AU
L49           489 SEA FILE=MEDLINE ABB=ON  PLU=ON  MA T?/AU
L61            29 SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND MEDLINE/LC
L67                SEL  PLU=ON  L61 1- CHEM :      132 TERMS
L68          6472 SEA FILE=MEDLINE ABB=ON  PLU=ON  L67
L88             0 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L48 OR L49) AND L68


=> s L51 or L88

L132           13 L51 OR L88

=> file embase

[redacted] ENTERED AT 12:39:03 ON 16 FEB 2006
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 FILE COVERS 1974 TO 9 Feb 2006 (20060209/ED)
```

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FILE COVERS 1907 - 16 Feb 2006 VOL 144 ISS 8
FILE LAST UPDATED: 15 Feb 2006 (20060215/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

http://www.cas.org/infopolicy.html
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE

=> d que nos L31

```
L7              STR
L9         101796 SEA FILE=REGISTRY SSS FUL L7
L10         11681 SEA FILE=CAPLUS ABB=ON  PLU=ON  L9
L28           379 SEA FILE=CAPLUS ABB=ON  PLU=ON  VERKMAN A?/AU
L29          1877 SEA FILE=CAPLUS ABB=ON  PLU=ON  MA T?/AU
L30            60 SEA FILE=CAPLUS ABB=ON  PLU=ON  L28 AND L29
L31             3 SEA FILE=CAPLUS ABB=ON  PLU=ON  L30 AND L10
```

=> d que nos L32

```
L11         10928 SEA FILE=CAPLUS ABB=ON  PLU=ON  CYSTIC?/OBI
L12         20440 SEA FILE=CAPLUS ABB=ON  PLU=ON  ?CYSTIC?/BI
L14          4392 SEA FILE=CAPLUS ABB=ON  PLU=ON  CFTR?/BI
L18           504 SEA FILE=CAPLUS ABB=ON  PLU=ON  ?FIBROCYSTIC?/BI
L19             1 SEA FILE=CAPLUS ABB=ON  PLU=ON  (?FIBRO CYSTIC?)/BI
L20         11128 SEA FILE=CAPLUS ABB=ON  PLU=ON  (?CYSTIC FIBRO?)/BI
L23         10507 SEA FILE=CAPLUS ABB=ON  PLU=ON  ION TRANSPORT/OBI
L25         62389 SEA FILE=CAPLUS ABB=ON  PLU=ON  ((ION? OR CHLOR?) (3A)
                  ?TRANSP?)/BI
L28           379 SEA FILE=CAPLUS ABB=ON  PLU=ON  VERKMAN A?/AU
L29          1877 SEA FILE=CAPLUS ABB=ON  PLU=ON  MA T?/AU
L30            60 SEA FILE=CAPLUS ABB=ON  PLU=ON  L28 AND L29
L32             8 SEA FILE=CAPLUS ABB=ON  PLU=ON  L30 AND (L11 OR L12 OR L14 OR
                  L18 OR L19 OR L20 OR L23 OR L25)
```

=> d que nos L90

```
L7              STR
L9         101796 SEA FILE=REGISTRY SSS FUL L7
L10         11681 SEA FILE=CAPLUS ABB=ON  PLU=ON  L9
L28           379 SEA FILE=CAPLUS ABB=ON  PLU=ON  VERKMAN A?/AU
L29          1877 SEA FILE=CAPLUS ABB=ON  PLU=ON  MA T?/AU
L90             8 SEA FILE=CAPLUS ABB=ON  PLU=ON  L10 AND (L28 OR L29)
```

=> s L31 or L32 or L90

```
L131           13 L31 OR L32 OR L90
```

```
Page 2-A
VAR G1=4/5
VAR G2=8-2 8-26/9-2 9-26
REP G20=(0-1) 12-11 12-10
NODE ATTRIBUTES:
NSPEC   IS R      AT   1
NSPEC   IS R      AT   2
NSPEC   IS R      AT   3
NSPEC   IS C      AT   4
NSPEC   IS C      AT   5
NSPEC   IS C      AT   6
NSPEC   IS C      AT   7
NSPEC   IS R      AT   8
NSPEC   IS R      AT   9
NSPEC   IS R      AT  10
NSPEC   IS R      AT  11
NSPEC   IS R      AT  12
NSPEC   IS C      AT  13
NSPEC   IS R      AT  14
NSPEC   IS R      AT  15
NSPEC   IS R      AT  16
NSPEC   IS R      AT  17
NSPEC   IS R      AT  18
NSPEC   IS R      AT  19
NSPEC   IS R      AT  20
NSPEC   IS R      AT  21
NSPEC   IS R      AT  22
NSPEC   IS R      AT  23
NSPEC   IS R      AT  24
NSPEC   IS R      AT  25
NSPEC   IS R      AT  26
CONNECT IS E3  RC AT   2
CONNECT IS E3  RC AT   3
CONNECT IS E1  RC AT   4
CONNECT IS E1  RC AT   5
DEFAULT MLEVEL IS ATOM
MLEVEL  IS CLASS  AT   4  5 13
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  26

STEREO ATTRIBUTES: NONE
L59          7067 SEA FILE=REGISTRY SUB=L9 SSS FUL L56

100.0% PROCESSED   10937 ITERATIONS                    7067 ANSWERS
SEARCH TIME: 00.00.01


=> => file caplus
FILE 'CAPLUS' ENTERED AT 12:38:56 ON 16 FEB 2006
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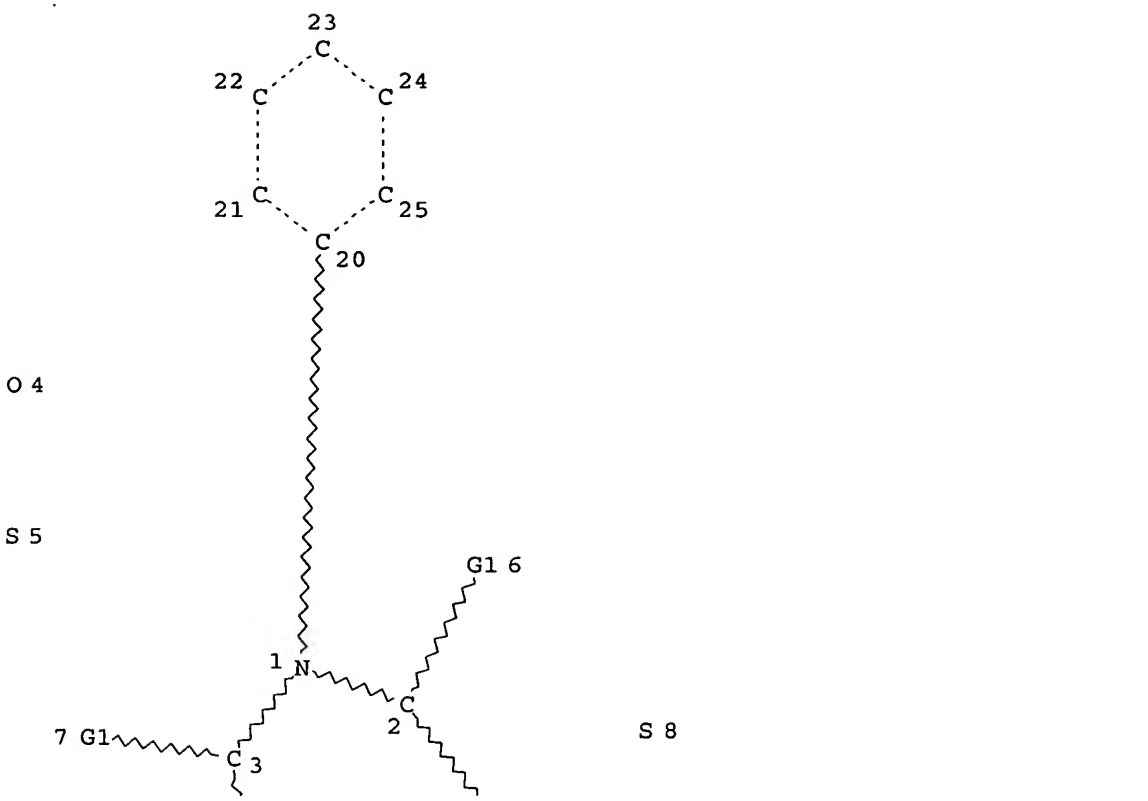
```

AUTHOR SEARCH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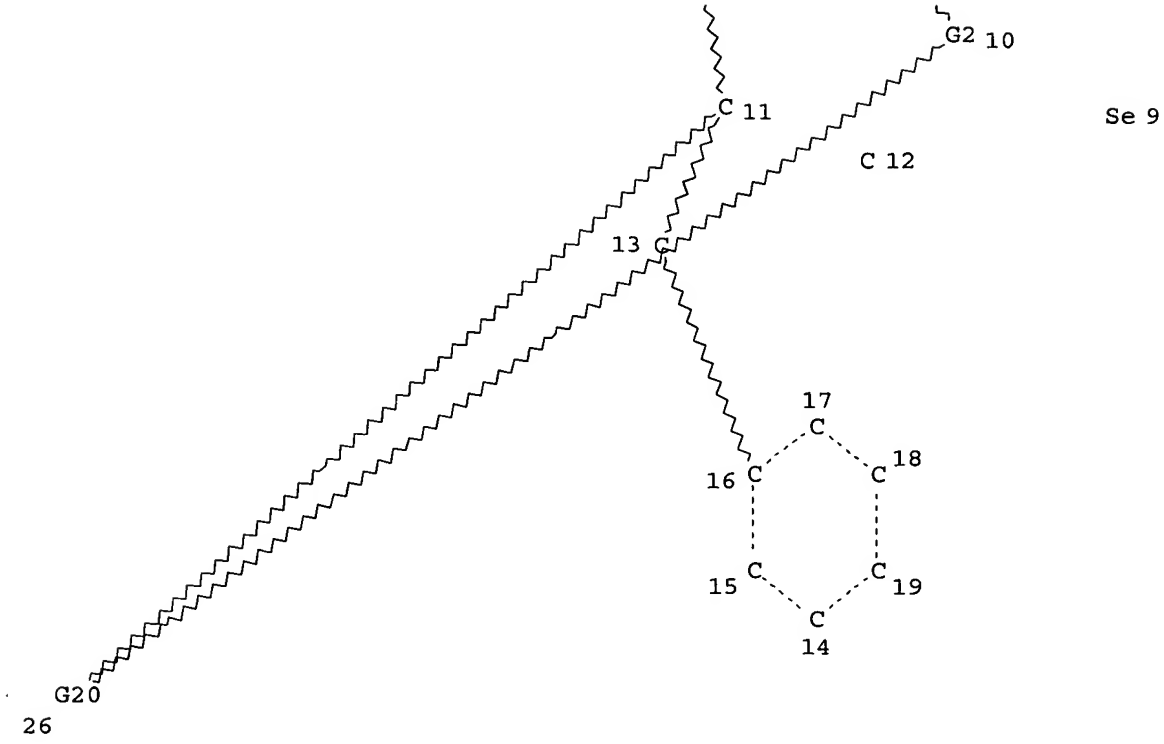
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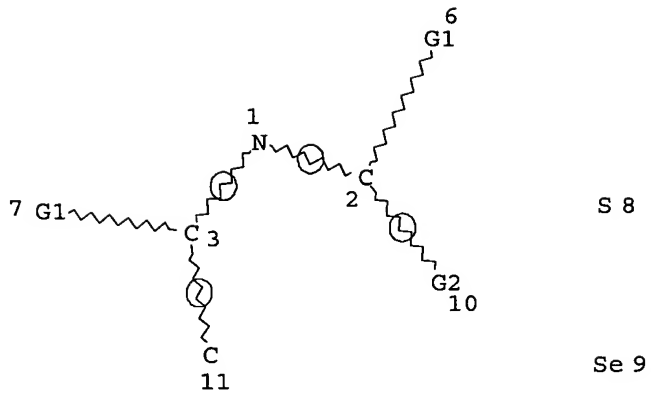

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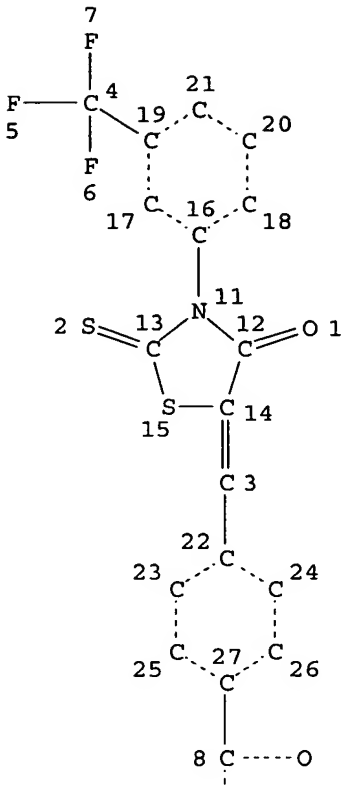

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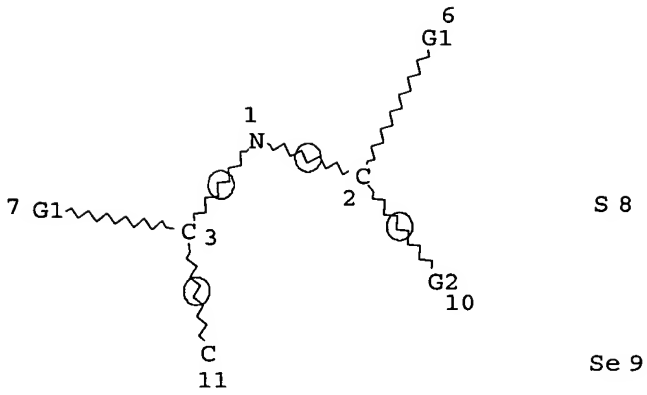
L7 STR

O 4

S 5



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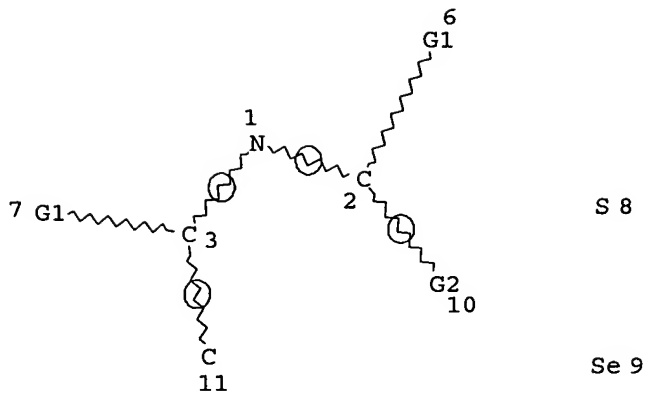

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STRUCTURE FILE UPDATES:   14 FEB 2006  HIGHEST RN 874270-88-9
DICTIONARY FILE UPDATES:  14 FEB 2006  HIGHEST RN 874270-88-9

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

*************************************************************************
*                                                                       *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                       *
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Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

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			US 2002-509049P	P	20020930
			US 2003-480253P	P	20030620
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OTHER SOURCE(S): MARPAT 140:247127

AB The invention provides compns., pharmaceutical prepns., and methods for inhibition of **cystic fibrosis** transmembrane conductance regulator protein (**CFTR**) that are useful for the study and treatment of **CFTR**-mediated diseases and conditions. The compns. and pharmaceutical prepns. of the invention may comprise one or more thiazolidinone compds., and may addnl. comprise one or more pharmaceutically acceptable carriers, excipients and/or adjuvants. The methods of the invention comprise, in certain embodiments, administering to a patient suffering from a **CFTR**-mediated disease or condition, an efficacious amount of a thiazolidinone compound In other embodiments the invention provides methods of inhibiting **CFTR** that comprise contacting cells in a subject with an effective amount of a thiazolidinone compound In addition, the invention features a non-human animal model of **CFTR**-mediated disease which model is produced by administration of a thiazolidinone compound to a non-human animal in an amount sufficient to inhibit **CFTR**.

IC ICM A61K031-549
INCL 514222500
CC 1-12 (Pharmacology)
Section cross-reference(s): 14, 63
ST thiazolidinone compd **cystic fibrosis** transmembrane conductance regulator protein inhibitor; **CFTR** inhibitor thiazolidinone compd therapeutic; **cystic fibrosis** disease animal model thiazolidinone compd
IT Biological **transport**
(**ion**; thiazolidinone compound **CFTR** inhibitors, uses, and animal model of **CFTR**-mediated disease)
IT Antidiarrheals
Aves
Cystic fibrosis
Diarrhea
Disease models
Drug delivery systems
Drug screening
Human
Mammalia
Primates

Rodentia
Structure-activity relationship
Ungulate
(thiazolidinone compound **CFTR** inhibitors, uses, and animal model of **CFTR**-mediated disease)

IT **CFTR** (**cystic fibrosis** transmembrane conductance regulator)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(thiazolidinone compound **CFTR** inhibitors, uses, and animal model of **CFTR**-mediated disease)

IT **141-84-4D**, 2-Thioxo-4-thiazolidinone, derivs. 28600-65-9D, Thiazolidinone, derivs. **292174-08-4**, 3-[(3-Trifluoromethyl)phenyl]-5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone **301308-44-1**, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone **303056-54-4 307510-92-5**, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone **328250-71-1**, 3-[(3-Trifluoromethyl)phenyl]-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone **535962-72-2**, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyoxyphenyl)methylene]-2-thioxo-4-thiazolidinone
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thiazolidinone compound **CFTR** inhibitors, uses, and animal model of **CFTR**-mediated disease)

IT 119-67-5, 2-Carboxybenzaldehyde 619-21-6, 3-Carboxybenzaldehyde 619-66-9, 4-Carboxybenzaldehyde **292174-03-9 671247-72-6 671247-73-7**
RL: RCT (Reactant); RACT (Reactant or reagent)
(thiazolidinone compound **CFTR** inhibitors, uses, and animal model of **CFTR**-mediated disease)

IT **141-84-4D**, 2-Thioxo-4-thiazolidinone, derivs. **292174-08-4**, 3-[(3-Trifluoromethyl)phenyl]-5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone **301308-44-1**, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone **303056-54-4 307510-92-5**, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone **328250-71-1**, 3-[(3-Trifluoromethyl)phenyl]-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone **535962-72-2**, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyoxyphenyl)methylene]-2-thioxo-4-thiazolidinone
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thiazolidinone compound **CFTR** inhibitors, uses, and animal model of **CFTR**-mediated disease)

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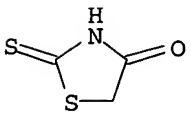

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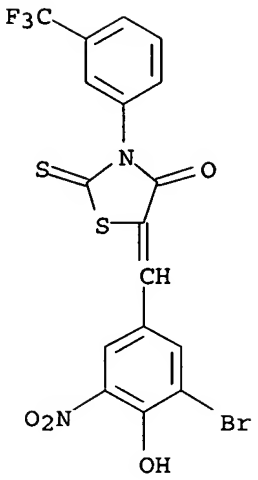

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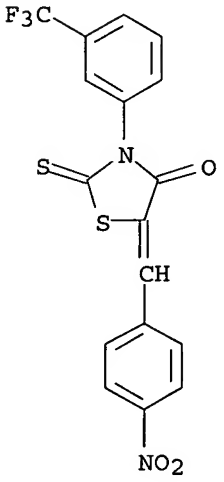

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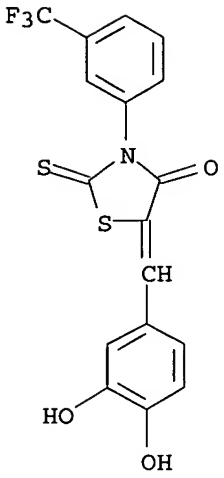

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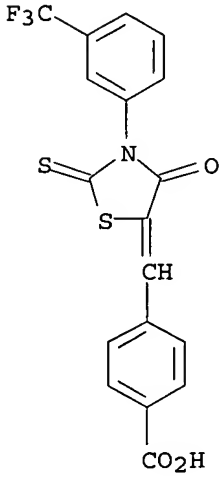

RN 328250-71-1 CAPLUS
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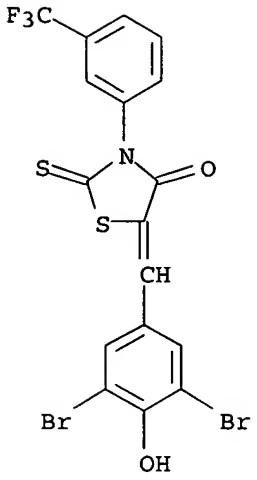

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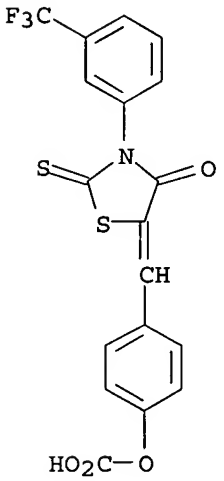
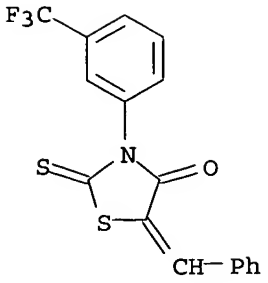


IT **292174-03-9 671247-72-6 671247-73-7**
RL: RCT (Reactant); RACT (Reactant or reagent)
(thiazolidinone compound **CFTR** inhibitors, uses, and animal model of **CFTR**-mediated disease)
RN 292174-03-9 CAPLUS
CN 4-Thiazolidinone, 5-(phenylmethylene)-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



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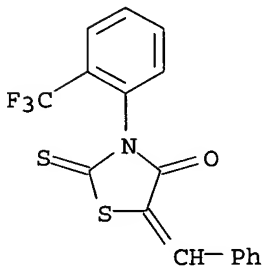

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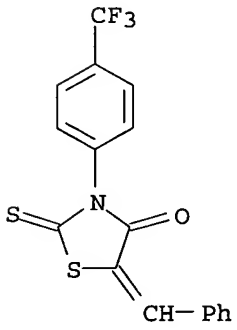


L136 ANSWER 3 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2004:189841 CAPLUS
DOCUMENT NUMBER: 141:254187
TITLE: Prevention of toxin-induced intestinal ion and fluid secretion by a small-molecule CFTR inhibitor
AUTHOR(S): Thiagarajah, Jay R.; Broadbent, Talmage; Hsieh, Emily; **Verkman, Alan S.**
CORPORATE SOURCE: Departments of Medicine and Physiology, Cardiovascular Research Institute, University of California, San Francisco, CA, USA

SOURCE: Gastroenterology (2004), 126(2), 511-519
CODEN: GASTAB; ISSN: 0016-5085
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background & Aims: The cystic fibrosis transmembrane conductance regulator (CFTR) provides an important apical route for Cl- secretion across intestinal epithelia. A thiazolidinone-type CFTR blocker (CFTRinh-172) reduced cholera toxin-induced fluid accumulation in mouse intestinal loops. Here, we characterize the efficacy and pharmacodynamics of CFTRinh-172 in blocking cAMP and cGMP induced Cl-/fluid secretion in rodent and human intestine. Methods & Results: CFTRinh-172 inhibited cAMP and cGMP agonist induced short-circuit current by >95% in T84 colonic epithelial cells (KI .apprx. 3 μmol/L) and in mouse and human intestinal sheets (KI .apprx. 9 μmol/L). A single i.p. injection of CFTRinh-172 (200 μg) blocked intestinal fluid secretion in a rat closed-loop model by >90% for cholera toxin and >70% for STa Escherichia coli toxin. In mice, CFTRinh-172 (20 μg) inhibited cholera toxin-induced intestinal fluid secretion by 90% (persistence t1/2 .apprx.10 h, KI .apprx. 5 μg) and STa toxin by 75% (KI .apprx. 10 μg). Tissue distribution and pharmacokinetic studies indicated intestinal CFTRinh-172 accumulation facilitated by enterohepatic circulation. An oral CFTRinh-172 preparation reduced fluid secretion by >90% in a mouse open-loop cholera model. Conclusions: A small mol. CFTR blocker markedly reduced intestinal ion and fluid secretion caused by cAMP/cGMP-dependent bacterial enterotoxins. CFTR inhibition may thus reduce fluid secretion in infectious secretory diarrheas.

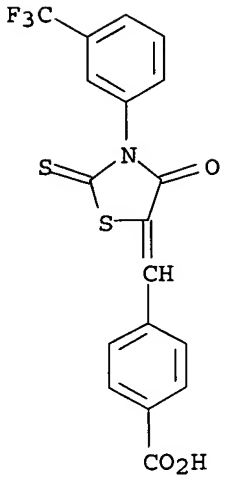
CC 1-9 (Pharmacology)

IT **307510-92-5**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thiazolidinone-type CFTR blocker CFTRinh-172 reduced intestinal ion and fluid secretion caused by cAMP/cGMP-dependent bacterial enterotoxin in rodent and human intestine without affecting intestinal fluid absorption)

IT **307510-92-5**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thiazolidinone-type CFTR blocker CFTRinh-172 reduced intestinal ion and fluid secretion caused by cAMP/cGMP-dependent bacterial enterotoxin in rodent and human intestine without affecting intestinal fluid absorption)

RN 307510-92-5 CAPLUS

CN Benzoic acid, 4-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinylidene]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 4 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2004:94932 CAPLUS
DOCUMENT NUMBER: 140:281314
TITLE: Altered channel gating mechanism for CFTR inhibition by a high-affinity thiazolidinone blocker
AUTHOR(S): Taddei, Alessandro; Folli, Chiara; Zegarra-Moran, Olga; Fanen, Pascale; **Verkman, A. S.**; Galietta, Luis J. V.
CORPORATE SOURCE: Laboratorio di Genetica Molecolare, Istituto Giannina Gaslini, Genoa, 16148, Italy
SOURCE: FEBS Letters (2004), 558(1-3), 52-56
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The thiazolidinone CFTRinh-172 was identified recently as a potent and selective blocker of the cystic fibrosis transmembrane conductance regulator (CFTR) Cl- channel. Here, we characterized the CFTRinh-172 inhibition mechanism by patch-clamp and short-circuit anal. using cells stably expressing wild-type and mutant CFTRs. CFTRinh-172 did not alter CFTR unitary conductance (8 pS), but reduced open probability by >90% with Ki≈0.6 μM. This effect was due to increased mean channel closed time without changing mean channel open time. Short-circuit current expts. indicated similar CFTRinh-172 inhibitory potency (Ki≈0.5 μM) for inhibition of Cl- current in wild-type, G551D, and G1349D CFTR; however, Ki was significantly reduced to 0.2 μM for ΔF508 CFTR. Our studies provide evidence for CFTR inhibition by CFTRinh-172 by a mechanism involving altered CFTR gating.

CC 1-12 (Pharmacology)
Section cross-reference(s): 14

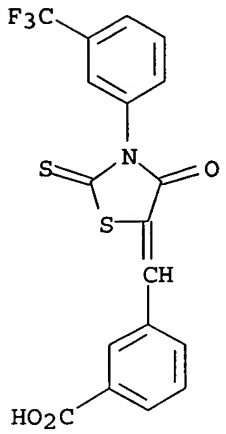
IT 28600-65-9D, Thiazolidinone, derivative **432526-28-8**
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(altered channel gating mechanism for CFTR inhibition by high-affinity thiazolidinone blocker)

IT **432526-28-8**
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU

(Therapeutic use); BIOL (Biological study); USES (Uses)
(altered channel gating mechanism for CFTR inhibition by high-affinity thiazolidinone blocker)

RN 432526-28-8 CAPLUS

CN Benzoic acid, 3-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinylidene]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 5 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 5

ACCESSION NUMBER: 2003:701956 CAPLUS

DOCUMENT NUMBER: 139:301298

TITLE: Nanomolar Affinity Small Molecule Correctors of Defective ΔF508- **CFTR** Chloride Channel Gating

AUTHOR(S): Yang, Hong; Shelat, Anang A.; Guy, R. Kiplin; Gopinath, Vadiraj S.; **Ma, Tonghui**; Du, Kai; Lukacs, Gergely L.; Taddei, Alessandro; Folli, Chiara; Pedemonte, Nicoletta; Galietta, Luis J. V.; **Verkman, A. S.**

CORPORATE SOURCE: Departments of Medicine and Physiology, University of California, San Francisco, CA, 94143, USA

SOURCE: Journal of Biological Chemistry (2003), 278(37), 35079-35085
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 139:301298

AB Deletion of Phe-508 (ΔF508) is the most common mutation in the **cystic fibrosis** transmembrane conductance regulator (**CFTR**) causing **cystic fibrosis.** ΔF508-**CFTR** has defects in both channel gating and endoplasmic reticulum-to-plasma membrane processing. We identified six novel classes of high affinity potentiators of defective ΔF508- **CFTR** Cl- channel gating by screening 100,000 diverse small mols. Compds. were added 15 min prior to assay of iodide uptake in epithelial cells co-expressing ΔF508- **CFTR** and a high sensitivity halide indicator (YFP-H148Q/I152L) in which ΔF508- **CFTR** was targeted to the plasma membrane by culture at 27° for 24 h.

Thirty-two compds. with submicromolar activating potency were identified; most had tetrahydrobenzothiophene, benzofuran, pyramidinetrione, dihydropyridine, and anthraquinone core structures (360-480 Da). Further screening of >1000 structural analogs revealed tetrahydrobenzothiophenes that activated ΔF508- **CFTR** Cl- conductance reversibly with Kd < 100 nM. Single-cell voltage clamp anal. showed characteristic **CFTR** currents after ΔF508- **CFTR** activation. Activation required low concns. of a cAMP agonist, thus mimicking the normal physiol. response. A Bayesian computational model was developed using tetrahydrobenzothiophene structure-activity data, yielding insight into the phys. character and structural features of active and inactive potentiators and successfully predicting the activity of structural analogs. Efficient potentiation of defective ΔF508- **CFTR** gating was also demonstrated in human bronchial epithelial cells from a ΔF508 **cystic fibrosis** subject after 27° temperature rescue. In conjunction with correctors of defective ΔF508- **CFTR** processing, small mol. potentiators of defective ΔF508- **CFTR** gating may be useful for therapy of **cystic fibrosis** caused by the ΔF508 mutation.

CC 1-3 (Pharmacology)

ST small mol corrector deltaF50CFTR chloride channel gating; **CFTR** mutant chloride channel gating small mol corrector

IT **CFTR** (**cystic fibrosis** transmembrane conductance regulator)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(508-dephenylalanine-; nanomolar affinity small mol. correctors of defective ΔF508- **CFTR** chloride channel gating in epithelial cells)

IT Electric current
(biol.; nanomolar affinity small mol. correctors of defective ΔF508- **CFTR** chloride channel gating in epithelial cells)

IT Epithelium
(bronchial; nanomolar affinity small mol. correctors of defective ΔF508- **CFTR** chloride channel gating in epithelial cells)

IT Biological transport
(channel-mediated; nanomolar affinity small mol. correctors of defective ΔF508- **CFTR** chloride channel gating in epithelial cells)

IT Biological **transport**
(**chloride**; preparation of tetrahydrobenzothiophene ΔF508- **CFTR** potentiators)

IT Bronchi
Thyroid gland
(epithelium; nanomolar affinity small mol. correctors of defective ΔF508- **CFTR** chloride channel gating in epithelial cells)

IT High throughput screening
Human
Structure-activity relationship
(nanomolar affinity small mol. correctors of defective ΔF508- **CFTR** chloride channel gating in epithelial cells)

IT Drug targets
(preparation of tetrahydrobenzothiophene ΔF508- **CFTR** potentiators)

IT Epithelium
(thyroid gland; nanomolar affinity small mol. correctors of defective ΔF508- **CFTR** chloride channel gating in epithelial cells)

IT Biological transport
(uptake, channel-mediated; nanomolar affinity small mol. correctors of defective ΔF508- **CFTR** chloride channel gating in epithelial cells)

IT 68217-75-4 68256-56-4 298193-32-5 303137-49-7 304685-77-6
312917-70-7 313262-43-0 313703-08-1 324577-00-6 345337-69-1
354547-94-7 420815-86-7 611183-37-0 611183-38-1
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
(nanomolar affinity small mol. correctors of defective ΔF508-**CFTR** chloride channel gating in epithelial cells)

IT 27285-13-8P 142995-02-6P 300712-63-4P 312925-57-8P 383379-36-0P
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(nanomolar affinity small mol. correctors of defective ΔF508-**CFTR** chloride channel gating in epithelial cells)

IT 609-65-4, Benzoyl chloride, 2-chloro- 638-29-9, Pentanoyl chloride 933-88-0, Benzoyl chloride, 2-methyl- 2040-76-8, Carbamic chloride, phenyl- 2719-27-9, Cyclohexanecarbonyl chloride 4524-93-0, Cyclopentanoyl chloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(nanomolar affinity small mol. correctors of defective ΔF508-**CFTR** chloride channel gating in epithelial cells)

IT 4815-28-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of tetrahydrobenzothiophene ΔF508- **CFTR** potentiators)

IT 16887-00-6, **Chloride**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**transport**; preparation of tetrahydrobenzothiophene ΔF508-**CFTR** potentiators)

IT 20461-54-5, Iodide, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(uptake; nanomolar affinity small mol. correctors of defective ΔF508- **CFTR** chloride channel gating in epithelial cells)

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 6 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 6

ACCESSION NUMBER: 2003:645706 CAPLUS
DOCUMENT NUMBER: 140:138711
TITLE: Benzoflavone activators of the **cystic fibrosis** transmembrane conductance regulator: towards a pharmacophore model for the nucleotide-binding domain
AUTHOR(S): Springsteel, Mark F.; Galietta, Luis J. V.; **Ma, Tonghui**; By, Kolbot; Berger, Gideon O.; Yang, Hong; Dicus, Christopher W.; Choung, Wonken; Quan, Chao; Shelat, Anang A.; Guy, R. Kiplin; **Verkman, A. S.**; Kurth, Mark J.; Nantz, Michael H.
CORPORATE SOURCE: Department of Chemistry, University of California, Davis, CA, 95616, USA
SOURCE: Bioorganic & Medicinal Chemistry (2003), 11(18), 4113-4120
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:138711

AB Our previous screen of flavones and related heterocycles for the ability to activate the **cystic fibrosis** transmembrane conductance regulator (**CFTR**) chloride channel indicated that UCCF-029, a 7,8-benzoflavone, was a potent activator. In the present

study, we describe the synthesis and evaluation, using cell-based assays, of a series of benzoflavone analogs to examine structure-activity relationships and to identify compds. having greater potency for activation of both wild type **CFTR** and a mutant **CFTR** (G551D-**CFTR**) that causes **cystic fibrosis** in some human subjects. Using UCCF-029 as a structural guide, a panel of 77 flavonoid analogs was prepared Anal. of the panel in FRT cells indicated that benzannulation of the flavone A-ring at the 7,8-position greatly improved compound activity and potency for several flavonoids. Incorporation of a B-ring pyridyl nitrogen either at the 3- or 4-position also elevated **CFTR** activity, but the influence of this structural modification was not as uniform as the influence of benzannulation. The most potent new analog, UCCF-339, activated wild-type **CFTR** with a Kd of 1.7 μM, which is more active than the previous most potent flavonoid activator of **CFTR**, apigenin. Several compds. in the benzoflavone panel also activated G551D-**CFTR**, but none were as active as apigenin. Pharmacophore modeling suggests a common binding mode for the flavones and other known **CFTR** activators at one of the nucleotide-binding sites, allowing for the rational development of more potent flavone analogs.

CC 1-3 (Pharmacology)

ST pharmacophore benzoflavone activator **CFTR** nucleotide binding domain

IT Human
Pharmacophores
Structure-activity relationship
(benzoflavone activators of **cystic fibrosis** transmembrane conductance regulator and pharmacophore model for nucleotide-binding domain)

IT **CFTR** (**cystic fibrosis** transmembrane conductance regulator)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(benzoflavone activators of **cystic fibrosis** transmembrane conductance regulator and pharmacophore model for nucleotide-binding domain)

IT Flavonoids
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzoflavone activators of **cystic fibrosis** transmembrane conductance regulator and pharmacophore model for nucleotide-binding domain)

IT 652138-03-9P 652138-07-3P
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(benzoflavone activators of **cystic fibrosis** transmembrane conductance regulator and pharmacophore model for nucleotide-binding domain)

IT 525-82-6, Flavone 604-59-1, UCCF 023 1645-20-1 1645-21-2 1744-33-8
1939-53-3 2110-25-0 3034-15-9 3034-16-0 3327-27-3 4143-74-2
6051-87-2 6051-88-3 14756-22-0 20525-20-6 53324-47-3 54197-90-9
71601-17-7 80309-04-2 98166-63-3 98166-64-4 98166-67-7
98166-69-9 98166-70-2 125240-02-0 133367-37-0 226547-98-4
226548-01-2 363608-67-7, UCCF-029 652137-98-9 652137-99-0
652138-00-6 652138-01-7 652138-02-8 652138-04-0 652138-05-1
652138-06-2 652138-08-4 652138-09-5 652138-10-8 652138-11-9
652138-12-0 652138-13-1 652138-14-2 652138-15-3 652138-16-4
652138-17-5 652138-18-6 652138-19-7 652138-20-0 652138-21-1
652138-22-2 652138-23-3 652138-24-4 652138-25-5 652138-26-6
652138-27-7 652138-28-8 652138-29-9 652138-30-2 652138-31-3

652138-32-4 652138-33-5 652138-34-6 652138-35-7 652138-36-8
652138-37-9 652138-38-0 652138-39-1 652138-40-4 652138-41-5
652138-42-6 652138-43-7 652138-44-8 652138-45-9
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzoflavone activators of **cystic fibrosis** transmembrane conductance regulator and pharmacophore model for nucleotide-binding domain)

IT 520-36-5, Apigenin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzoflavone activators of **cystic fibrosis** transmembrane conductance regulator and pharmacophore model for nucleotide-binding domain)

IT 2110-30-7 14254-57-0, Isonicotinoyl chloride 52220-64-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(benzoflavone activators of **cystic fibrosis** transmembrane conductance regulator and pharmacophore model for nucleotide-binding domain)

IT 652138-46-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(benzoflavone activators of **cystic fibrosis** transmembrane conductance regulator and pharmacophore model for nucleotide-binding domain)

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 7 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 2003:521329 CAPLUS
DOCUMENT NUMBER: 139:254727
TITLE: 3-(2-benzyloxyphenyl)isoxazoles and isoxazolines: synthesis and evaluation as **CFTR** activators
AUTHOR(S): Sammelson, Robert E.; **Ma, T.**; Galietta, Luis J. V.; **Verkman, A. S.**; Kurth, Mark J.
CORPORATE SOURCE: Department of Chemistry, University of California, Davis, CA, 95616-5295, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2003), 13(15), 2509-2512
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 139:254727

AB A novel class of activators for chloride conductance in the **cystic fibrosis** transmembrane conductance regulator (**CFTR**) protein has been identified. These 3-(2-benzyloxyphenyl)isoxazoles and 3-(2-benzyloxyphenyl)isoxazolines were synthesized employing the 1,3-dipolar cycloaddn. of nitrile oxides with various alkene and alkyne dipolarophiles. Utilizing a fluorescence cell-based assay of halide transport, the best compds. increased **CFTR**-dependent **chloride transport** with half-maximal stimulation at 20-50 μM.

CC 1-3 (Pharmacology)

ST benzyloxyphenylisoxazole isoxazoline prepn **cystic fibrosis** transmembrane conductance regulator activator; combinatorial library design benzyloxyphenylisoxazole isoxazoline **CFTR** activator **chloride transport**

IT Combinatorial library
Cystic fibrosis

Drug design
Pharmacophores
(benzyloxyphenyl isoxazoles and isoxazolines synthesis and evaluation as **CFTR** activators)

IT **CFTR** (**cystic fibrosis** transmembrane conductance regulator)
Chloride channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(benzyloxyphenyl isoxazoles and isoxazolines synthesis and evaluation as **CFTR** activators)

IT Structure-activity relationship
(**chloride transport**-stimulating; benzyloxyphenyl isoxazoles and isoxazolines synthesis and evaluation as **CFTR** activators)

IT Biological **transport**
(**chloride**; benzyloxyphenyl isoxazoles and isoxazolines synthesis and evaluation as **CFTR** activators)

IT 363608-67-7, UCCF 029
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(UCCF 029; benzyloxyphenyl isoxazoles and isoxazolines synthesis and evaluation as **CFTR** activators)

IT 226070-80-0, UCCF 180
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(UCCF 180; benzyloxyphenyl isoxazoles and isoxazolines synthesis and evaluation as **CFTR** activators)

IT 600740-19-0P 600740-20-3P 600740-21-4P 600740-22-5P 600740-23-6P
600740-24-7P 600740-25-8P 600740-26-9P 600740-27-0P 600740-28-1P
600740-29-2P 600740-30-5P 600740-31-6P 600740-32-7P 600740-33-8P
600740-34-9P 600740-35-0P 600740-36-1P 600740-37-2P 600740-38-3P
600740-44-1P
RL: CPN (Combinatorial preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); CMBI (Combinatorial study); PREP (Preparation); USES (Uses)
(benzyloxyphenyl isoxazoles and isoxazolines synthesis and evaluation as **CFTR** activators)

IT 107-19-7, Propargyl alcohol 135-02-4, 2-Methoxybenzaldehyde 624-65-7, Propargyl chloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(benzyloxyphenyl isoxazoles and isoxazolines synthesis and evaluation as **CFTR** activators)

IT 29577-53-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(benzyloxyphenyl isoxazoles and isoxazolines synthesis and evaluation as **CFTR** activators)

IT 345967-78-4P 600740-15-6P 600740-16-7P 600740-17-8P 600740-18-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(benzyloxyphenyl isoxazoles and isoxazolines synthesis and evaluation as **CFTR** activators)

IT 255-59-4, Quinolizinium 446-72-0, Genistein 520-36-5, Apigenin 43135-91-7, Benzimidazolone 601519-76-0, UCCF 152
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzyloxyphenyl isoxazoles and isoxazolines synthesis and evaluation as **CFTR** activators)

IT 16887-00-6, **Chloride**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**transport**; benzyloxyphenyl isoxazoles and isoxazolines synthesis and evaluation as **CFTR** activators)

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 8 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 2003:561548 CAPLUS
DOCUMENT NUMBER: 139:391085
TITLE: **CFTR** activation in human bronchial epithelial cells by novel benzoflavone and benzimidazolone compounds
AUTHOR(S): Caci, Emanuela; Folli, Chiara; Zegarra-Moran, Olga; **Ma, Tonghui**; Springsteel, Mark F.; Sammelson, Robert E.; Nantz, Michael H.; Kurth, Mark J.; **Verkman, A. S.**; Galietta, Luis J. V.
CORPORATE SOURCE: Laboratorio di Genetica Molecolare, Istituto Giannina Gaslini, Genoa, 16148, Italy
SOURCE: American Journal of Physiology (2003), 285(1, Pt. 1), L180-L188
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Activators of the **CFTR** Cl- channel may be useful for therapy of **cystic fibrosis.** Short-circuit current (Isc) measurements were done on human bronchial epithelial cells to characterize the best flavone and benzimidazolone **CFTR** activators identified by lead-based combinatorial synthesis and high-throughput screening. The 7,8-benzoflavone UCCF-029 was a potent activator of Cl- transport, with activating potency (<1 μM) being much better than other flavones, such as apigenin. The benzimidazolone UCCF-853 gave similar Isc but with lower potency (5-20 μM). In combination, the effect induced by maximal UCCF-029 and UCCF-853 was 50-80% greater than that of either compound alone. The apparent activating potencies (Kd) of UCCF-029, UCCF-853, and apigenin increased strongly with increasing basal **CFTR** activity: for example, Kd for activation by UCCF-029 decreased from >5 to <0.4 μM with increasing basal Isc from .apprx.4 μA/cm2 to .apprx.12 μA/cm2. This dependence was confirmed in permeabilized Fischer rat thyroid cells stably expressing **CFTR.** Our results demonstrate efficacy of novel **CFTR** activators in bronchial epithelia and provide evidence that activating potency depends on basal **CFTR** activity.

CC 1-9 (Pharmacology)
Section cross-reference(s): 13
ST benzoflavone benzimidazole bronchi epithelium **chloride transport**
IT **Cystic fibrosis**
Human
(**CFTR** activation in human bronchial epithelial cells by novel benzoflavone and benzimidazolone compds.)
IT **CFTR** (**cystic fibrosis** transmembrane conductance regulator)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**CFTR** activation in human bronchial epithelial cells by novel benzoflavone and benzimidazolone compds.)
IT Epithelium
(bronchial; **CFTR** activation in human bronchial epithelial cells by novel benzoflavone and benzimidazolone compds.)
IT Bronchi
(epithelium; **CFTR** activation in human bronchial epithelial cells by novel benzoflavone and benzimidazolone compds.)
IT Biological **transport**
(of **chloride ion**; **CFTR** activation in human bronchial epithelial cells by novel benzoflavone and benzimidazolone compds.)

IT 520-36-5, Apigenin 363608-67-7, UCCF-029 625458-06-2, UCCF 853
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**CFTR** activation in human bronchial epithelial cells by novel benzoflavone and benzimidazolone compds.)
IT 16887-00-6, **Chloride ion**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**transport**; **CFTR** activation in human bronchial epithelial cells by novel benzoflavone and benzimidazolone compds.)
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 9 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 9
ACCESSION NUMBER: 2002:742984 CAPLUS
DOCUMENT NUMBER: 138:313909
TITLE: High-affinity Activators of **Cystic Fibrosis** Transmembrane Conductance Regulator (**CFTR**) Chloride Conductance Identified by High-Throughput Screening
AUTHOR(S): **Ma, Tonghui**; Vetrivel, L.; Yang, Hong; Pedemonte, Nicoletta; Zegarra-Moran, Olga; Galietta, Luis J. V.; **Verkman, A. S.**
CORPORATE SOURCE: Departments of Medicine and Physiology, Cardiovascular Research Institute, University of California, San Francisco, CA, 94143-0521, USA
SOURCE: Journal of Biological Chemistry (2002), 277(40), 37235-37241
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Cystic fibrosis** (CF) is caused by mutations in the CF transmembrane conductance regulator (**CFTR**) protein that reduce cAMP-stimulated Cl- conductance in airway and other epithelia. The purpose of this investigation was to identify new classes of potent **CFTR** activators. A collection of 60,000 diverse drug-like compds. was screened at 10 μm together with a low concentration of forskolin (0.5 μm) in Fisher rat thyroid epithelial cells co-expressing human **CFTR** and a green fluorescent protein-based Cl- sensor. Primary screening yielded 57 strong activators (greater activity than reference compound apigenin), most of which were unrelated in chemical structure to known **CFTR** activators, and 284 weaker activators. Secondary anal. of the strong activators included anal. of **CFTR** specificity, forskolin requirement, transepithelial short-circuit current, activation kinetics, dose response, toxicity, and activation mechanism. Three compds., the most potent being a dihydroisoquinoline, activated **CFTR** by elevating cellular cAMP, probably by phosphodiesterase inhibition. Fourteen compds. activated **CFTR** without cAMP elevation or phosphatase inhibition, suggesting direct **CFTR** interaction. The most potent compds. had tetrahydrocarbazol, hydroxycoumarin, and thiazolidine core structures. These compds. induced **CFTR** Cl- currents rapidly (<5 min) with Kd down to 200 nm and were **CFTR**-selective, reversible, and nontoxic. Several compds., the most potent being a trifluoromethylphenylbenzamine, activated the CF-causing mutant G551D, but with much weaker affinity (Kd > 10 μm). When added for 10 min, none of the compds. activated ΔPhe508-**CFTR** in transfected cells grown at 37° (with ΔPhe508-**CFTR** trapped in the endoplasmic reticulum). However, after

correction of trafficking by 48 h of growth at 27°, tetrahydrocarbazol and N-phenyltriazine derivs. strongly stimulated Cl- conductance with Kd < 1 μm. The new activators identified here may be useful in defining mol. mechanisms of **CFTR** activation and as lead compds. in CF drug development.

CC 1-3 (Pharmacology)

ST **cystic fibrosis** transmembrane conductance regulator activator high throughput screening; chloride conductance **CFTR** activator high throughput screening

IT Human
(**CFTR** activators effect on short-circuit current in human bronchial epithelial cells; high-affinity activators of **cystic fibrosis** transmembrane conductance regulator (**CFTR**) chloride conductance identified by high-throughput screening)

IT Epithelium
(bronchial, **CFTR** activators effect on short-circuit current in human bronchial epithelial cells; high-affinity activators of **cystic fibrosis** transmembrane conductance regulator (**CFTR**) chloride conductance identified by high-throughput screening)

IT Biological **transport**
(**chloride**; high-affinity activators of **cystic fibrosis** transmembrane conductance regulator (**CFTR**) chloride conductance identified by high-throughput screening)

IT Bronchi
(epithelium, **CFTR** activators effect on short-circuit current in human bronchial epithelial cells; high-affinity activators of **cystic fibrosis** transmembrane conductance regulator (**CFTR**) chloride conductance identified by high-throughput screening)

IT **Cystic fibrosis**
Drug screening
High throughput screening
Structure-activity relationship
(high-affinity activators of **cystic fibrosis** transmembrane conductance regulator (**CFTR**) chloride conductance identified by high-throughput screening)

IT **CFTR** (**cystic fibrosis** transmembrane conductance regulator)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(wildtype and mutant; high-affinity activators of **cystic fibrosis** transmembrane conductance regulator (**CFTR**) chloride conductance identified by high-throughput screening)

IT 16887-00-6, Chloride, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(high-affinity activators of **cystic fibrosis** transmembrane conductance regulator (**CFTR**) chloride conductance identified by high-throughput screening)

IT 51334-86-2 58926-60-6 68301-50-8 297159-83-2 301337-99-5 303227-10-3 307511-63-3 316361-05-4 337497-45-7 361182-76-5 403735-81-9 425400-78-8 512205-03-7 512205-04-8 512205-05-9 512205-06-0 512205-07-1
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(high-affinity activators of **cystic fibrosis** transmembrane conductance regulator (**CFTR**) chloride conductance identified by high-throughput screening)

IT 60-92-4, CAMP 9013-05-2, Phosphatase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(high-affinity activators of **cystic fibrosis**

transmembrane conductance regulator (**CFTR**) chloride conductance identified by high-throughput screening and cAMP induction or phosphatase inhibition involvement in action mechanism)

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 10 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 10

ACCESSION NUMBER: 2002:932809 CAPLUS

DOCUMENT NUMBER: 139:235

TITLE: Thiazolidinone **CFTR** inhibitor identified by high-throughput screening blocks cholera toxin-induced intestinal fluid secretion

AUTHOR(S): **Ma, Tonghui**; Thiagarajah, Jay R.; Yang, Hong; Sonawane, Nitin D.; Folli, Chiara; Galietta, Luis J. V.; **Verkman, A. S.**

CORPORATE SOURCE: Department of Medicine, Cardiovascular Research Institute, University of California, San Francisco, San Francisco, CA, 94143-0521, USA

SOURCE: Journal of Clinical Investigation (2002), 110(11), 1651-1658
CODEN: JCINAO; ISSN: 0021-9738

PUBLISHER: American Society for Clinical Investigation

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Secretory diarrhea is the leading cause of infant death in developing countries and a major cause of morbidity in adults. The **cystic fibrosis** transmembrane conductance regulator (**CFTR**) protein is required for fluid secretion in the intestine and airways and, when defective, causes the lethal genetic disease **cystic fibrosis.** We screened 50,000 chemical diverse compds. for inhibition of cAMP/flavone-stimulated Cl- transport in epithelial cells expressing **CFTR.** Six **CFTR** inhibitors of the 2-thioxo-4-thiazolidinone chemical class were identified. The most potent compound discovered by screening of structural analogs, **CFTRinh**-172, reversibly inhibited **CFTR** short-circuit current in less than 2 min in a voltage-independent manner with K1 approx. 300 nM. **CFTRinh**-172 was nontoxic at high concns. in cell culture and mouse models. At concns. fully inhibiting **CFTR**, **CFTRinh**-172 did not prevent elevation of cellular cAMP or inhibit non-**CFTR** Cl- channels, multidrug resistance protein-1 (MDR-1), ATP-sensitive K+ channels, or a series of other transporters. A single i.p. injection of **CFTRinh**-172 (250 μg/kg) in mice reduced by more than 90% cholera toxin-induced fluid secretion in the small intestine over 6 h. Thiazolidinone **CFTR** inhibitors may be useful in developing large-animal models of **cystic fibrosis** and in reducing intestinal fluid loss in cholera and other secretory diarrheas.

CC 1-1 (Pharmacology)

ST intestine fluid secretion thiazolidinone **CFTR** inhibitor; high throughput screening thiazolidinone **CFTR** inhibitor

IT Biological **transport**
(**chloride**; thiazolidinone **CFTR** inhibitor identified by high-throughput screening blocks cholera toxin-induced intestinal fluid secretion)

IT Diarrhea
(secretory; thiazolidinone **CFTR** inhibitor identified by high-throughput screening blocks cholera toxin-induced intestinal fluid secretion)

IT Drug screening
Epithelium
High throughput screening

(thiazolidinone **CFTR** inhibitor identified by high-throughput screening blocks cholera toxin-induced intestinal fluid secretion)

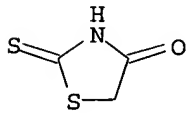
IT **CFTR** (**cystic fibrosis** transmembrane conductance regulator)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(thiazolidinone **CFTR** inhibitor identified by high-throughput screening blocks cholera toxin-induced intestinal fluid secretion)

IT **141-84-4D**, 2-Thioxo-4-thiazolidinone, derivs. **292174-08-4** **301308-44-1** **303056-54-4** **307510-92-5** **328250-71-1** **535962-72-2**
RL: PAC (Pharmacological activity); BIOL (Biological study)
(thiazolidinone **CFTR** inhibitor identified by high-throughput screening blocks cholera toxin-induced intestinal fluid secretion)

IT 16887-00-6, **Chloride**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**transport**; thiazolidinone **CFTR** inhibitor identified by high-throughput screening blocks cholera toxin-induced intestinal fluid secretion)

IT **141-84-4D**, 2-Thioxo-4-thiazolidinone, derivs. **292174-08-4** **301308-44-1** **303056-54-4** **307510-92-5** **328250-71-1** **535962-72-2**
RL: PAC (Pharmacological activity); BIOL (Biological study)
(thiazolidinone **CFTR** inhibitor identified by high-throughput screening blocks cholera toxin-induced intestinal fluid secretion)

RN 141-84-4 CAPLUS
CN 4-Thiazolidinone, 2-thioxo- (9CI) (CA INDEX NAME)



RN 292174-08-4 CAPLUS
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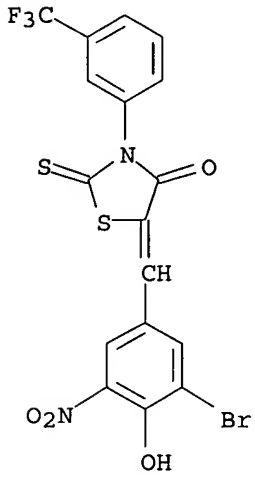
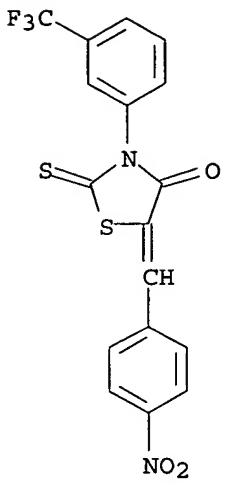
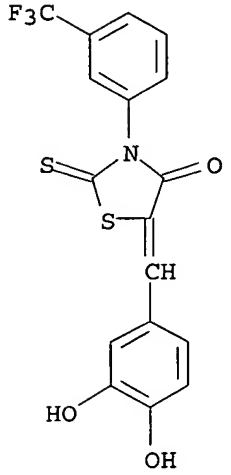


RN 301308-44-1 CAPLUS
CN 4-Thiazolidinone, 5-[(4-nitrophenyl)methylene]-2-thioxo-3-[3-

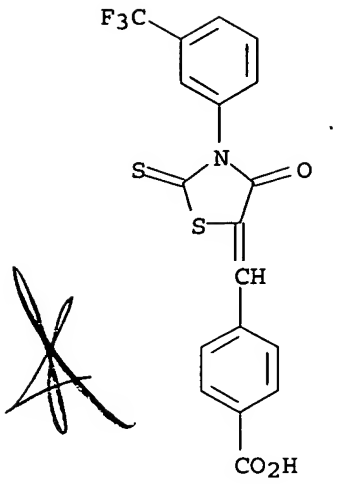
(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



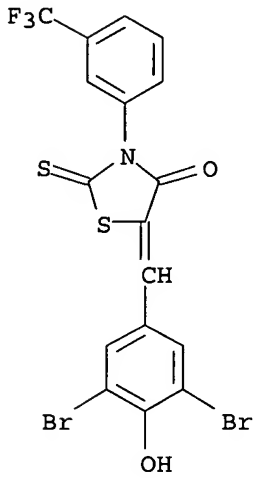
RN 303056-54-4 CAPLUS
CN 4-Thiazolidinone, 5-[(3,4-dihydroxyphenyl)methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



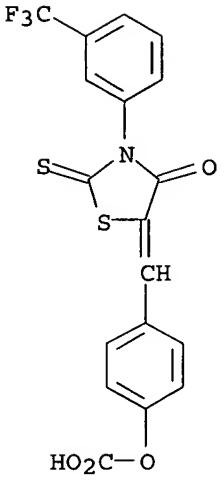
RN 307510-92-5 CAPLUS
CN Benzoic acid, 4-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinylidene]methyl]- (9CI) (CA INDEX NAME)



RN 328250-71-1 CAPLUS
CN 4-Thiazolidinone, 5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



RN 535962-72-2 CAPLUS
CN 4-Thiazolidinone, 5-[[4-(carboxyoxy)phenyl]methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

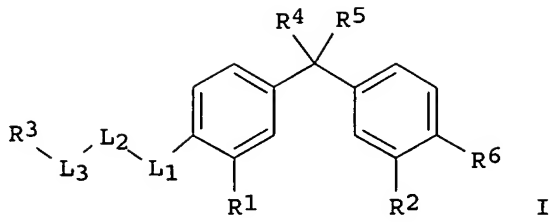
L136 ANSWER 11 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:467841 CAPLUS
DOCUMENT NUMBER: 141:38355
TITLE: Preparation of non-secosteroidal diaryl compounds as vitamin D receptor modulators for the treatment of bone disease, psoriasis, and other related diseases
INVENTOR(S): Bunel, Emilio Enrique; Gajewski, Robert Peter; Jones, Charles David; Lu, Jianliang; **Ma, Tianwei**; Nagpal, Sunil; Yee, Ying Kwong
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 355 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004048309	A1	20040610	WO 2003-US35055	20031120
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2506891	AA	20040610	CA 2003-2506891	20031120
EP 1565422	A1	20050824	EP 2003-781741	20031120
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, BG, CZ, EE, HU, SK				

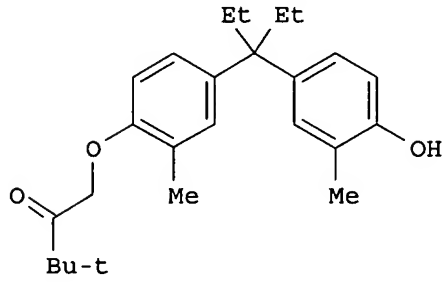
PRIORITY APPLN. INFO.: US 2002-429041P P 20021122
WO 2003-US35055 W 20031120

OTHER SOURCE(S): MARPAT 141:38355

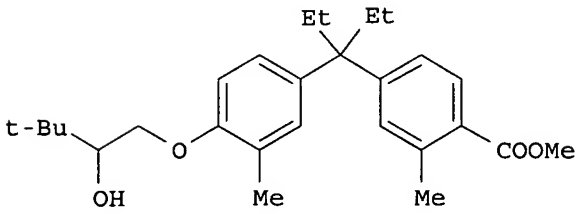
GI



I



II



III

AB The present invention relates to the preparation of novel, non-secosteroidal, diaryl compds. I (R1 and R2 are independently H, F, Cl, CF3, CH2F, CHF2, OMe, OEt, vinyl, Me, Et, Pr, 1-methylethyl, 1,1-dimethylethyl, Bu, 1-methylpropyl, 2-methylpropyl or cyclopropyl; R3 = 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl or substituted pentyls; R4 and R5 are independently Me, Et, Pr, or 1-methylethyl; L1 = O, CH2, C(O), CHOH, CH(Me), or C(Me)OH; L2 = CH2, C(O), CHOH, CH(Me), or C(Me)OH; or L1 and L2 as a group = CH2-CH2, CH:CH, Or C:C; L3 = CH2, C(O), CHOH, CH(Me), or C(Me)OH; R6 = subtituted carboxylic acids, esters and amide) as vitamin D receptor modulators for the treatment of bone disease, psoriasis, and other related diseases. Thus, o-cresol, 3-pentanone, and methanesulfonic acid were reacted to give 3',3'-Bis[4-hydroxy-3-methylphenyl]pentane which was treated with 3,3-dimethyl-1-bromo-2-butanone to give II. II was treated with Tf2O to give the corresponding triflate, followed by reduction of the ketone to the alc. using NaBH4. The alc. was treated with Pd(OAc)2, Dppf, MeOH, Et3N, DMF, and pressurized carbon monoxide (1,000 psi) for 48 h to give III which had an EC50 of 21 nm in an OCN promoter assay.

IC ICM C07C059-90
ICS C07C062-24; C07C069-78; C07C235-34; C07C311-50; C07C317-28; C07D257-06; C07D277-34; A61K031-12; A61K031-165; A61K031-18; A61K031-19; A61K031-192; A61K031-235; A61K031-41; A61K031-426

CC 23-9 (Aliphatic Compounds)
Section cross-reference(s): 1, 63

IT 700831-68-1P 700831-69-2P 700831-70-5P 700831-71-6P 700831-72-7P
700831-73-8P 700831-74-9P 700831-75-0P 700831-76-1P 700831-77-2P
700831-78-3P 700831-79-4P 700831-80-7P 700831-81-8P 700831-82-9P
700831-83-0P 700831-84-1P 700831-85-2P 700831-86-3P 700831-87-4P

700831-88-5P 700831-89-6P 700831-90-9P 700831-91-0P 700831-92-1P
700831-93-2P 700831-94-3P 700831-95-4P 700831-96-5P 700831-97-6P
700831-98-7P 700831-99-8P 700832-00-4P 700832-01-5P 700832-02-6P
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700832-27-5P 700832-68-4P 700833-12-1P 700833-13-2P 700833-14-3P
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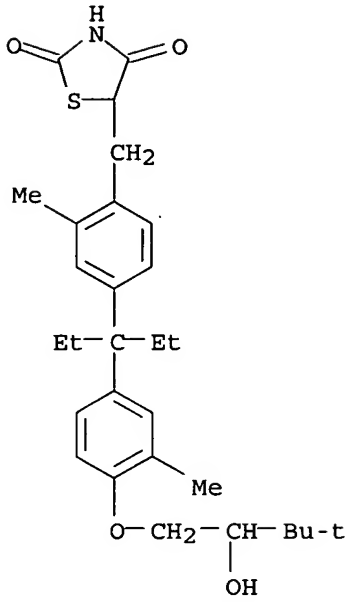
700833-30-3P 700833-31-4P 700833-32-5P 700833-33-6P 700833-34-7P
700833-35-8P 700833-36-9P 700833-36-9P **700833-37-0P**
700840-88-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of diaryl vitamin D receptor modulators for treatment of bone disease, psoriasis and other implicated diseases)

IT 55041-27-5P 233268-82-1P 700832-32-2P 700832-34-4P 700832-39-9P
700832-41-3P 700832-42-4P 700832-43-5P 700832-44-6P 700832-46-8P
700832-48-0P 700832-50-4P 700832-51-5P 700832-53-7P 700832-55-9P
700832-56-0P 700832-58-2P 700832-60-6P 700832-62-8P 700832-63-9P
700832-64-0P 700832-66-2P 700832-69-5P 700832-72-0P 700832-73-1P
700832-74-2P 700832-75-3P 700832-76-4P 700832-77-5P 700832-78-6P
700832-79-7P 700832-80-0P 700832-82-2P 700832-83-3P 700832-84-4P
700832-85-5P 700832-86-6P **700832-87-7P** 700832-88-8P
700832-89-9P **700832-90-2P** 700832-91-3P 700832-92-4P
700832-93-5P 700833-38-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of diaryl vitamin D receptor modulators for treatment of bone disease, psoriasis and other implicated diseases)

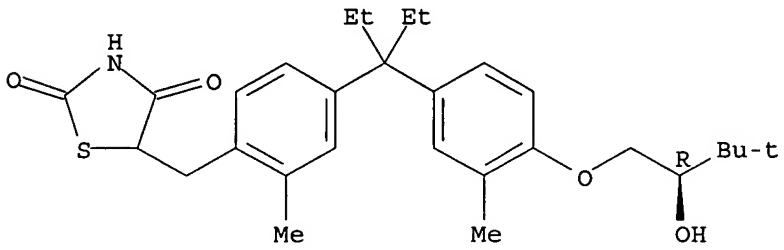
IT **700832-20-8P 700833-37-0P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of diaryl vitamin D receptor modulators for treatment of bone disease, psoriasis and other implicated diseases)

RN 700832-20-8 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[1-ethyl-1-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]propyl]-2-methylphenyl]methyl]- (9CI) (CA INDEX NAME)



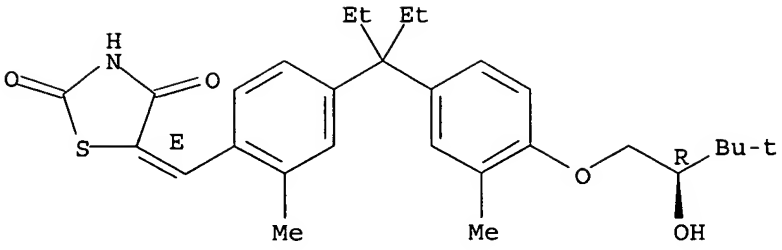
RN 700833-37-0 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[1-ethyl-1-[4-[(2R)-2-hydroxy-3,3-dimethylbutoxy]-3-methylphenyl]propyl]-2-methylphenyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



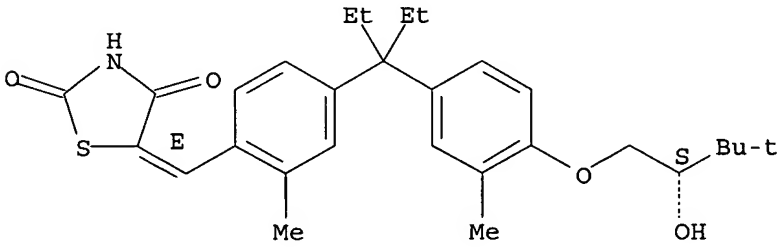
IT **700832-87-7P 700832-90-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of diaryl vitamin D receptor modulators for treatment of bone disease, psoriasis and other implicated diseases)
RN 700832-87-7 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[1-ethyl-1-[4-[(2R)-2-hydroxy-3,3-dimethylbutoxy]-3-methylphenyl]propyl]-2-methylphenyl]methylene]-, (5E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 700832-90-2 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[1-ethyl-1-[4-[(2S)-2-hydroxy-3,3-dimethylbutoxy]-3-methylphenyl]propyl]-2-methylphenyl]methylene]-, (5E)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 12 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:290483 CAPLUS
DOCUMENT NUMBER: 140:315071
TITLE: Thiazolidinone **cystic fibrosis** transmembrane conductance regulator protein inhibitors and pharmaceutical prepns. for treatment of **CFTR**-mediated diseases and conditions
INVENTOR(S): **Verkman, Alan; Ma, Tonghui**
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004028480	A2	20040408	WO 2003-US31005	20030930
WO 2004028480	A3	20040701		

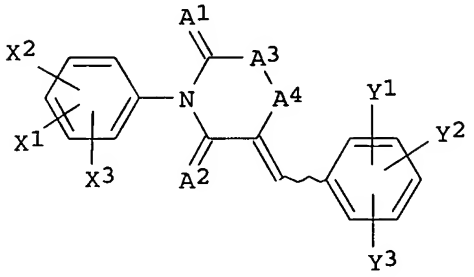
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004063695	A1	20040401	US 2002-262573		20020930
CA 2500498	AA	20040408	CA 2003-2500498		20030930
US 2004235800	A1	20041125	US 2003-676727		20030930
EP 1549321	A2	20050706	EP 2003-798805		20030930
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2003014943	A	20050802	BR 2003-14943		20030930
JP 2006503853	T2	20060202	JP 2004-540305		20030930
PRIORITY APPLN. INFO.:			US 2002-262573	A	20020930
			US 2002-509049P	P	20020930
			US 2003-480253P	P	20030620
			WO 2003-US31005	W	20030930

OTHER SOURCE(S): MARPAT 140:315071

GI



I

AB The invention discloses compns., pharmaceutical prepns. and methods for inhibition of **cystic fibrosis** transmembrane conductance regulator protein (**CFTR**) that are useful for the study and treatment of **CFTR**-mediated diseases and conditions. The compns. and pharmaceutical prepns. of the invention may comprise one or more thiazolidinone compds. I (X1-X3, Y1-Y3=H, organic group, halo, nitro, azo, OH, mercapto; A1, A2=O, S; A3=S, Se; A4= ≥1 C or heteroatom or is absent), and may addnl. comprise one or more pharmaceutically acceptable carriers, excipients and/or adjuvants. The methods of the invention comprise, in certain embodiments, administering to a patient suffering from a **CFTR**-mediated disease or condition, an efficacious amount of a thiazolidinone compound In other embodiments the invention provides methods of inhibiting **CFTR** that comprise contacting cells in a subject with an effective amount of a thiazolidinone compound In addition, the invention features a non-human animal model of **CFTR**-mediated disease which model is produced by administration of a thiazolidinone compound to a non-human animal in an amount sufficient to inhibit **CFTR**.

IC ICM A61K

CC 1-9 (Pharmacology)
Section cross-reference(s): 14, 28, 63

ST **cystic fibrosis** transmembrane conductance regulator protein inhibitor thiazolidine deriv

IT Potassium channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ATP-sensitive; thiazolidinone **cystic fibrosis** transmembrane conductance regulator protein inhibitors and

pharmaceutical prepns. for treatment of **CFTR**-mediated diseases and conditions)

IT Diarrhea
(antidiarrheal; thiazolidinone **cystic fibrosis** transmembrane conductance regulator protein inhibitors and pharmaceutical prepns. for treatment of **CFTR**-mediated diseases and conditions)

IT Intestine
(colon, mucosa; thiazolidinone **cystic fibrosis** transmembrane conductance regulator protein inhibitors and pharmaceutical prepns. for treatment of **CFTR**-mediated diseases and conditions)

IT Biological **transport**
(**ion, CFTR**; thiazolidinone **cystic fibrosis** transmembrane conductance regulator protein inhibitors and pharmaceutical prepns. for treatment of **CFTR**-mediated diseases and conditions)

IT Antidiarrheals
Aves
Cystic fibrosis
Disease models
Drug bioavailability
Drug delivery systems
Drug screening
Human
Intestinal juice
Primates
Rodentia
(thiazolidinone **cystic fibrosis** transmembrane conductance regulator protein inhibitors and pharmaceutical prepns. for treatment of **CFTR**-mediated diseases and conditions)

IT **CFTR** (**cystic fibrosis** transmembrane conductance regulator)
Chloride channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(thiazolidinone **cystic fibrosis** transmembrane conductance regulator protein inhibitors and pharmaceutical prepns. for treatment of **CFTR**-mediated diseases and conditions)

IT **677027-75-7P**
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(thiazolidinone **cystic fibrosis** transmembrane conductance regulator protein inhibitors and pharmaceutical prepns. for treatment of **CFTR**-mediated diseases and conditions)

IT **307510-92-5P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(thiazolidinone **cystic fibrosis** transmembrane conductance regulator protein inhibitors and pharmaceutical prepns. for treatment of **CFTR**-mediated diseases and conditions)

IT 504-78-9D, Thiazolidine, derivs. **292174-08-4**, 3-[(3-Trifluoromethyl)phenyl]-5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone **301308-44-1**, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone **303056-54-4 328250-71-1**, 3-[(3-Trifluoromethyl)phenyl]-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone **535962-72-2**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

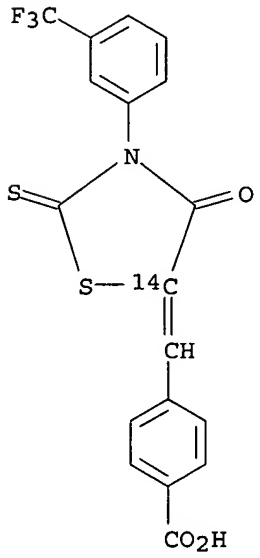
(Biological study); USES (Uses)
(thiazolidinone **cystic fibrosis** transmembrane conductance regulator protein inhibitors and pharmaceutical prepns. for treatment of **CFTR**-mediated diseases and conditions)

IT 98-16-8 121-44-8, Triethylamine, reactions 619-66-9, 4-Carboxybenzaldehyde 50718-91-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(thiazolidinone **cystic fibrosis** transmembrane conductance regulator protein inhibitors and pharmaceutical prepns. for treatment of **CFTR**-mediated diseases and conditions)

IT **677027-74-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(thiazolidinone **cystic fibrosis** transmembrane conductance regulator protein inhibitors and pharmaceutical prepns. for treatment of **CFTR**-mediated diseases and conditions)

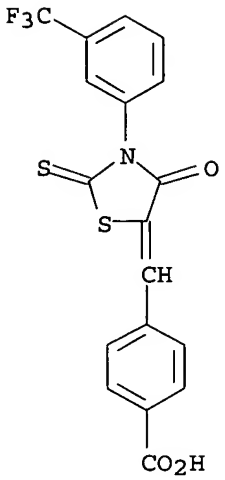
IT **677027-75-7P**
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(thiazolidinone **cystic fibrosis** transmembrane conductance regulator protein inhibitors and pharmaceutical prepns. for treatment of **CFTR**-mediated diseases and conditions)

RN 677027-75-7 CAPLUS
CN Benzoic acid, 4-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinylidene-5-14C]methyl]- (9CI) (CA INDEX NAME)



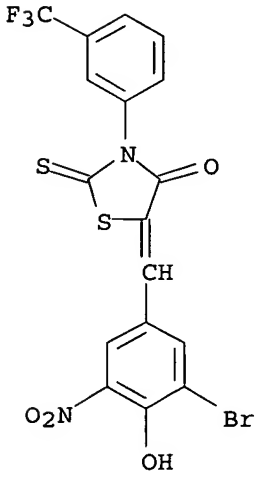
IT **307510-92-5P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(thiazolidinone **cystic fibrosis** transmembrane conductance regulator protein inhibitors and pharmaceutical prepns. for treatment of **CFTR**-mediated diseases and conditions)

RN 307510-92-5 CAPLUS
CN Benzoic acid, 4-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinylidene]methyl]- (9CI) (CA INDEX NAME)

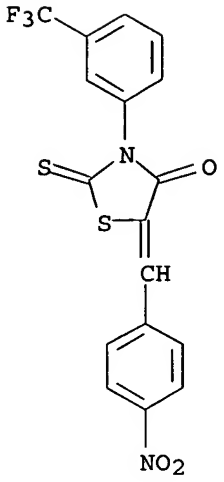


IT **292174-08-4**, 3-[(3-Trifluoromethyl)phenyl]-5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone **301308-44-1**, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone **303056-54-4 328250-71-1**, 3-[(3-Trifluoromethyl)phenyl]-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone **535962-72-2**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thiazolidinone **cystic fibrosis** transmembrane conductance regulator protein inhibitors and pharmaceutical prepns. for treatment of **CFTR**-mediated diseases and conditions)

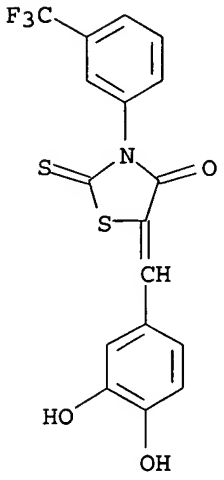
RN 292174-08-4 CAPLUS
CN 4-Thiazolidinone, 5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



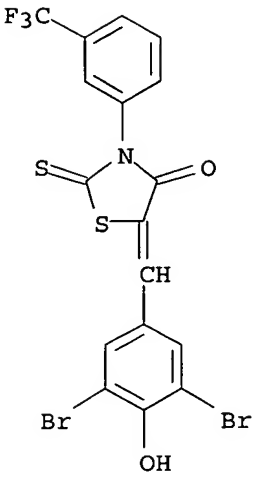
RN 301308-44-1 CAPLUS
CN 4-Thiazolidinone, 5-[(4-nitrophenyl)methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



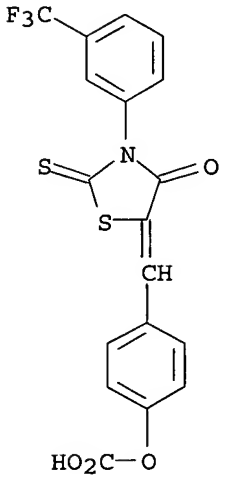
RN 303056-54-4 CAPLUS
CN 4-Thiazolidinone, 5-[(3,4-dihydroxyphenyl)methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



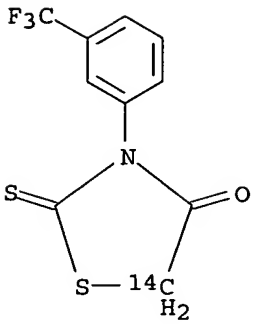
RN 328250-71-1 CAPLUS
CN 4-Thiazolidinone, 5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



RN 535962-72-2 CAPLUS
CN 4-Thiazolidinone, 5-[[4-(carboxyoxy)phenyl]methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



IT **677027-74-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(thiazolidinone **cystic fibrosis** transmembrane conductance regulator protein inhibitors and pharmaceutical prepns. for treatment of **CFTR**-mediated diseases and conditions)
RN 677027-74-6 CAPLUS
CN 4-Thiazolidinone-5-14C, 2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



L136 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:506016 CAPLUS
DOCUMENT NUMBER: 141:236485
TITLE: Synthesis and characterization of a small molecule CFTR chloride channel inhibitor
AUTHOR(S): He, Cheng-yan; Zhang, Heng-jun; Su, Zhong-min; Zhou, Jin-song; Yang, Hong; **Ma, Tong-hui**
CORPORATE SOURCE: Membrane Channel Research Laboratory, Northeast Normal University, Changchun, 130024, Peop. Rep. China
SOURCE: Chemical Research in Chinese Universities (2004), 20(3), 334-337
CODEN: CRCUED; ISSN: 1005-9040
PUBLISHER: Higher Education Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A thiazolidinone CFTR inhibitor (CFTRinh-172) was synthesized by a three-step procedure with trifluoromethylaniline as the starting material. The synthesized CFTR inhibitor was characterized structurally by 1H-NMR and functionally in a CFTR-expressing cell line FRT/hCFTR/EYFP-H148Q by both fluorescent and electrophysiol. methods. A large amount (100 g) of high-quality small mol. thiazolidinone CFTR chloride channel inhibitor, CFTRinh-172, can be produced with this simple three-step synthetic procedure. The structure of the final product 2-thioxo-3-(3-trifluoromethylphenyl)-5-[4-carboxyphenyl-methylene]-4-thiazolidinone was confirmed by 1H NMR. The overall yield was 58% with a purity over 99% as analyzed by HPLC. The synthesized CFTRinh-172 specifically inhibited CFTR chloride channel function in a cell-based fluorescence assay (Kd≈1.5 μmol/L) and in a Ussing chamber-based short-circuit current assay (Kd≈0.2 μmol/L), indicating better quality than that of the com. combinatorial compound The synthesized inhibitor is nontoxic to cultured cells at a high concentration and to mouse at a high dose. The synthetic procedure developed here can be used to produce a large amount of the high-quality CFTRinh-172 suitable for antidiarrheal studies and for creation of cystic fibrosis models in large animals. The procedure can be used to synthesize radiolabeled CFTRinh-172 for in vivo pharmacokinetics studies.

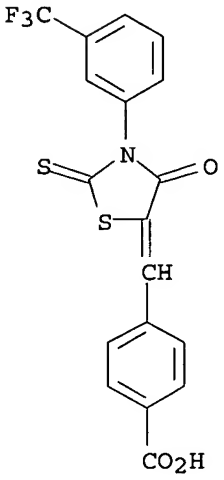
CC 1-12 (Pharmacology)
IT **307510-92-5P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and characterization of a small mol. CFTR chloride channel inhibitor)
IT **315-08-2P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and characterization of a small mol. CFTR chloride channel inhibitor)

IT **307510-92-5P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and characterization of a small mol. CFTR chloride channel inhibitor)

RN 307510-92-5 CAPLUS

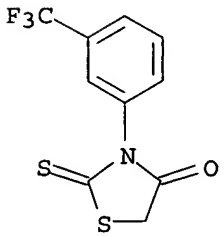
CN Benzoic acid, 4-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinylidene]methyl]- (9CI) (CA INDEX NAME)



IT **315-08-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and characterization of a small mol. CFTR chloride channel inhibitor)

RN 315-08-2 CAPLUS

CN 4-Thiazolidinone, 2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 14 OF 23 MEDLINE on STN
ACCESSION NUMBER: 2005158340 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15790911
TITLE: CFTR-regulated chloride transport at the ocular surface in living mice measured by potential differences.
AUTHOR: Levin Marc H; **Verkman A S**
CORPORATE SOURCE: Department of Medicine, Cardiovascular Research Institute, University of California San Francisco, San Francisco, California, USA.
CONTRACT NUMBER: DK35124 (NIDDK)
EB00415 (NIBIB)
EY13574 (NEI)
HL59198 (NHLBI)
HL73856 (NHLBI)
SOURCE: Investigative ophthalmology & visual science, (2005 Apr) 46 (4) 1428-34.
Journal code: 7703701. ISSN: 0146-0404.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200505
ENTRY DATE: Entered STN: 20050326
Last Updated on STN: 20050513
Entered Medline: 20050512

ABSTRACT:
PURPOSE: To define the role of the cystic fibrosis transmembrane conductance regulator (CFTR) in Cl(-) secretion at the mouse ocular surface in vivo. METHODS: Open-circuit potential differences (PDs) across the fluid-bathed ocular surface were measured in anesthetized wild-type and cystic fibrosis (CF) mice in response to Cl(-) ion substitution and transport agonists and inhibitors. RESULTS: Basal ocular surface PD was -23 +/- 1 mV (SE; 20 wild-type mice), depolarizing to -16 +/- 2 mV after amiloride, then hyperpolarizing to -34 +/- 3 mV after low Cl(-). CFTR activation by forskolin or a selective activator caused further sustained hyperpolarization to -50 to -60 mV. UTP produced a comparable but transient hyperpolarization. The CFTR inhibitors CFTR(inh)-172 and GlyH-101 largely reversed agonist- but not low Cl(-)-induced hyperpolarizations. PD in CF mice hyperpolarized by 2.1 mV after low Cl(-) and was insensitive to CFTR activators or inhibitors. CONCLUSIONS: CFTR provides a major pathway for mouse ocular surface Cl(-) secretion, suggesting the application of CFTR activators as therapy for dry eye. Amiloride-sensitive Na(+) transporters facilitate Na(+) absorption. PD measurements provide a robust and reproducible means of assessing ocular surface ion transporting mechanisms.

CONTROLLED TERM: Amiloride: PD, pharmacology
Animals
Benzoic Acids: PD, pharmacology
*Chlorides: ME, metabolism
*Conjunctiva: ME, metabolism
*Cornea: ME, metabolism
Cystic Fibrosis Transmembrane Conductance Regulator: AI, antagonists & inhibitors
*Cystic Fibrosis Transmembrane Conductance Regulator: PH, physiology
Epithelial Cells: ME, metabolism
Forskolin: PD, pharmacology
Ion Transport
Membrane Potentials: DE, drug effects
Mice
Mice, Inbred CFTR

Mice, Mutant Strains
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Thiazoles: PD, pharmacology
CAS REGISTRY NO.: 126880-72-6 (Cystic Fibrosis Transmembrane Conductance Regulator); 2609-46-3 (Amiloride); 66428-89-5 (Forskolin)
CHEMICAL NAME: 0 (3-((3-trifluoromethyl)phenyl)-5-((3-carboxyphenyl)methylene)-**2-thioxo-4-thiazolidinone**); 0 (Benzoic Acids); 0 (Chlorides); 0 (Thiazoles)

L136 ANSWER 15 OF 23 MEDLINE on STN
ACCESSION NUMBER: 2004505131 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15246976
TITLE: CFTR involvement in nasal potential differences in mice and pigs studied using a thiazolidinone CFTR inhibitor.
AUTHOR: Salinas Danieli B; Pedemonte Nicoletta; Muanprasat Chatchai; Finkbeiner Walter F; Nielson Dennis W; **Verkman A S**
CORPORATE SOURCE: Department of Medicine and Physiology, Cardiovascular Research Institute, University of California, San Francisco, California 94143, USA.
CONTRACT NUMBER: DK-35124 (NIDDK)
EB-00415 (NIBIB)
EY-13574 (NEI)
HL-59198 (NHLBI)
HL-73856 (NHLBI)
SOURCE: American journal of physiology. Lung cellular and molecular physiology, (2004 Nov) 287 (5) L936-43. Electronic Publication: 2004-07-09.
Journal code: 100901229. ISSN: 1040-0605.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200411
ENTRY DATE: Entered STN: 20041013
Last Updated on STN: 20041219
Entered Medline: 20041119

ABSTRACT:
Nasal potential difference (PD) measurements have been used to demonstrate defective CFTR function in cystic fibrosis (CF) and to evaluate potential CF therapies. We used the selective thiazolidinone CFTR inhibitor CFTR(inh)-172 to define the involvement of CFTR in nasal PD changes in mice and pigs. In normal mice infused intranasally with a physiological saline solution containing amiloride, nasal PD was -4.7 +/- 0.7 mV, hyperpolarizing by 15 +/- 1 mV after a low-Cl- solution, and a further 3.9 +/- 0.5 mV after forskolin. CFTR(inh)-172 produced 1.1 +/- 0.9- and 4.3 +/- 0.7-mV depolarizations when added after low Cl- and forskolin, respectively. Systemically administered CFTR(inh)-172 reduced the forskolin-induced hyperpolarization from 4.7 +/- 0.4 to 0.9 +/- 0.1 mV but did not reduce the low Cl(-)-induced hyperpolarization. Nasal PD was -12 +/- 1 mV in CF mice after amiloride, changing by <0.5 mV after low Cl- or forskolin. In pigs, nasal PD was -14 +/- 3 mV after amiloride, hyperpolarizing by 13 +/- 2 mV after low Cl- and a further 9 +/- 1 mV after forskolin. CFTR(inh)-172 and glibenclamide did not affect nasal PD in pigs. Our results suggest that cAMP-dependent nasal PDs in mice primarily involve CFTR-mediated Cl- conductance, whereas cAMP-independent PDs are produced by a different, but CFTR-dependent, Cl- channel. In pigs, CFTR may not be responsible for Cl- channel-dependent nasal PDs. These results have important implications for interpreting nasal PDs in terms of CFTR function in animal

models of CFTR activation and inhibition.
CONTROLLED TERM: Check Tags: Female; Male
4,4'-Diisothiocyanostilbene-2,2'-Disulfonic Acid: PD, pharmacology
Amiloride: PD, pharmacology
Animals
*Benzoic Acids: PD, pharmacology
*Cystic Fibrosis Transmembrane Conductance Regulator: AI, antagonists & inhibitors
Cystic Fibrosis Transmembrane Conductance Regulator: GE, genetics
*Cystic Fibrosis Transmembrane Conductance Regulator: ME, metabolism
Diuretics: PD, pharmacology
Forskolin: PD, pharmacology
Glyburide: PD, pharmacology
Hypoglycemic Agents: PD, pharmacology
Membrane Potentials: DE, drug effects
Mice
Mice, Inbred CFTR
Nasal Mucosa: DE, drug effects
*Nasal Mucosa: ME, metabolism
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Sus scrofa
*Thiazoles: PD, pharmacology
CAS REGISTRY NO.: 10238-21-8 (Glyburide); 126880-72-6 (Cystic Fibrosis Transmembrane Conductance Regulator); 2609-46-3 (Amiloride); 53005-05-3 (4,4'-Diisothiocyanostilbene-2,2'-Disulfonic Acid); 66428-89-5 (Forskolin)
CHEMICAL NAME: 0 (3-((3-trifluoromethyl)phenyl)-5-((3-carboxyphenyl)methylene)-2-**thioxo**-**4-thiazolidinone**); 0 (Benzoic Acids); 0 (Diuretics); 0 (Hypoglycemic Agents); 0 (Thiazoles)

L136 ANSWER 16 OF 23 MEDLINE on STN
ACCESSION NUMBER: 2004220901 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15001557
TITLE: A small molecule CFTR inhibitor produces cystic fibrosis-like submucosal gland fluid secretions in normal airways.
AUTHOR: Thiagarajah Jay R; Song Yuanlin; Haggie Peter M; **Verkman A S**
CORPORATE SOURCE: Department of Medicine, Cardiovascular Research Institute, University of California, San Francisco, California, USA.
SOURCE: FASEB journal : official publication of the Federation of American Societies for Experimental Biology, (2004 May) 18 (7) 875-7. Electronic Publication: 2004-03-04.
Journal code: 8804484. ISSN: 1530-6860.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200409
ENTRY DATE: Entered STN: 20040505
Last Updated on STN: 20040929
Entered Medline: 20040928
ABSTRACT:
Airway submucosal glands have been proposed as a primary site for initiating and sustaining airway disease in cystic fibrosis (CF). However, it has been

difficult to define the role of CFTR in gland fluid secretion because of concerns in interpreting experiments on diseased CF human airways subjected to chronic infection and inflammation. Here, we test the role of CFTR in gland fluid secretion by using a selective CFTR inhibitor (CFTRinh-172) in pig and human airways. Measurements of single-gland fluid secretion rates showed inhibition of both cholinergic and cAMP-stimulated fluid secretion by CFTRinh-172. Secreted fluid [Na+] and [Cl-] measured by fluorescence ratio imaging were 101 and 116 mM, respectively, and not significantly altered by secretory agonists or CFTR inhibition. Gland fluid pH was 7.1 and reduced by 0.4 units after CFTR inhibition. Gland fluid viscosity, determined by photobleaching of FITC-dextran, was threefold increased in pilocarpine-stimulated gland fluid after CFTR inhibition, and protein concentration was increased from 12 to 20 mg/ml. Our data provide strong evidence that gland fluid secretion is CFTR-dependent. The relatively hyper-viscous and acidic fluid secretions produced by acute CFTR inhibition support a role for defective gland function in CF lung disease and provide a rational basis for pharmacological creation of a large animal model of CF.

CONTROLLED TERM: Animals
*Benzoic Acids: PD, pharmacology
Body Fluids: CH, chemistry
*Body Fluids: SE, secretion
*Bronchi: DE, drug effects
Bronchi: SE, secretion
Cells, Cultured: DE, drug effects
Cells, Cultured: SE, secretion
Chlorides: ME, metabolism
Cholinergic Agents: PD, pharmacology
Cyclic AMP: PH, physiology
Cystic Fibrosis: PA, pathology
*Cystic Fibrosis: PP, physiopathology
Cystic Fibrosis Transmembrane Conductance Regulator: AI, antagonists & inhibitors
*Cystic Fibrosis Transmembrane Conductance Regulator: DE, drug effects
Cystic Fibrosis Transmembrane Conductance Regulator: PH, physiology
*Exocrine Glands: DE, drug effects
Exocrine Glands: SE, secretion
Forskolin: PD, pharmacology
Humans
Hydrogen-Ion Concentration
Pilocarpine: PD, pharmacology
Second Messenger Systems: DE, drug effects
Sodium: ME, metabolism
Swine
Thapsigargin: PD, pharmacology
*Thiazoles: PD, pharmacology
Viscosity

CAS REGISTRY NO.: 126880-72-6 (Cystic Fibrosis Transmembrane Conductance Regulator); 60-92-4 (Cyclic AMP); 66428-89-5 (Forskolin); 67526-95-8 (Thapsigargin); 7440-23-5 (Sodium); 92-13-7 (Pilocarpine)

CHEMICAL NAME: 0 (3-((3-trifluoromethyl)phenyl)-5-((3-carboxyphenyl)methylene)-**2-thioxo-4-thiazolidinone**); 0 (Benzoic Acids); 0 (Chlorides); 0 (Cholinergic Agents); 0 (Thiazoles)

L136 ANSWER 17 OF 23 MEDLINE on STN
ACCESSION NUMBER: 92118790 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1310027

TITLE: Protein kinase A dependent membrane protein phosphorylation and chloride conductance in endosomal vesicles from kidney cortex.
AUTHOR: Reenstra W W; Sabolic I; Bae H R; **Verkman A S**
CORPORATE SOURCE: Research Institute, Children's Hospital, Oakland, California 94609.
CONTRACT NUMBER: DK35124 (NIDDK)
DK39354 (NIDDK)
HL42368 (NHLBI)
SOURCE: Biochemistry, (1992 Jan 14) 31 (1) 175-81.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199202
ENTRY DATE: Entered STN: 19920315
Last Updated on STN: 19920315
Entered Medline: 19920225

ABSTRACT:
Regulation of Cl conductance by protein kinase A may play a role in control of endosomal acidification [Bae, H.-R., & Verkman, A. S. (1990) Nature, 348, 637-639]. To investigate the mechanism of kinase A action, cell-free measurements of Cl transport and membrane protein phosphorylation were carried out in apical endocytic vesicles from rabbit kidney proximal tubule. Cl transport was measured by a stopped-flow quenching assay in endosomes labeled in vivo with the fluorescent Cl indicator 6-methoxy-N-(3-sulfopropyl)quinolinium. Phosphorylation was studied in a purified endosomal preparation by SDS-PAGE and autoradiography of membrane proteins labeled by [gamma-32P]ATP. Endosomes had a permeability (PCl) for conductive Cl transport of 3.1 x 10(-8) cm/s at 23 degrees C which was stilbene inhibitable. PCl was increased by 90 +/- 20% by a 10-min preincubation with the catalytic subunit of kinase A (PKA, 10 units/mL) and MgATP (0.5 mM) with anion selectivity Cl greater than I greater than Br. The increase in PCl was blocked by 100 microM N-[2-(methylamino)ethyl]-5-isoquinolinesulfonamide (**H-8**) and was reversed by addition of alkaline phosphatase (AP, 40 units/mL) after incubation with PKA and MgATP; the increase in PCl was not blocked by pretreatment with AP.(ABSTRACT TRUNCATED AT 250 WORDS)

CONTROLLED TERM: Check Tags: Comparative Study
Animals
Chloride Channels
*Chlorides: ME, metabolism
Enzyme Activation: DE, drug effects
Kidney Cortex: EN, enzymology
*Kidney Cortex: ME, metabolism
Kidney Tubules, Proximal: EN, enzymology
*Membrane Proteins: ME, metabolism
Molecular Weight
Phosphoproteins: AN, analysis
Phosphorylation
*Protein Kinases: ME, metabolism
Rabbits
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Stilbenes: PD, pharmacology
CHEMICAL NAME: 0 (Chloride Channels); 0 (Chlorides); 0 (Membrane Proteins); 0 (Phosphoproteins); 0 (Stilbenes); EC 2.7.1.37 (Protein Kinases)

L136 ANSWER 18 OF 23 MEDLINE on STN

ACCESSION NUMBER: 91039283 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2172546
TITLE: Urea transport in freshly isolated and cultured cells from rat inner medullary collecting duct.
AUTHOR: Zhang R B; **Verkman A S**
CORPORATE SOURCE: Department of Medicine, University of California, San Francisco 94143-0532.
CONTRACT NUMBER: DK35124 (NIDDK)
DK39354 (NIDDK)
HL42368 (NHLBI)
SOURCE: Journal of membrane biology, (1990 Sep) 117 (3) 253-61.
Journal code: 0211301. ISSN: 0022-2631.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199012
ENTRY DATE: Entered STN: 19910208
Last Updated on STN: 19970203
Entered Medline: 19901211

ABSTRACT:
Regulation of urea transport by vasopressin in inner medullary collecting duct (IMCD) cells is thought to be important for the urinary concentrating mechanism. Isolated tubule perfusion studies suggest the existence of a saturable urea carrier. We have measured 14C-urea efflux in IMCD cells which were freshly isolated and grown in primary culture. Cells were isolated from rat papilla by collagenase digestion and hypotonic shock. In suspended cells, 14C-urea efflux (Jurea) from loaded cells was exponential with time constant 59 +/- 3 sec (SEM, n = 6, 23 degrees C). Jurea had an activation energy of 4.1 kcal/mole and was inhibited 42 +/- 7% by 0.25 mM phloretin and 30-40% by the high affinity urea analogues dimethylurea and phenylurea. Jurea was increased 40-60% by addition of vasopressin (10(-8) M) or 8-bromo-cAMP (1 mM); stimulated Jurea was inhibited 55 +/- 8% by the kinase A inhibitor **H-8**
. Phorbol esters and epidermal growth factor did not alter Jurea. IMCD cells grown in primary culture were homogeneous in appearance with greater than fivefold stimulation of cAMP by vasopressin. The exponential time constant for urea efflux was 610 +/- 20 sec (n = 3). Jurea was not altered by vasopressin, cAMP or phloretin. Another function of in vivo IMCD cells, vasopressin-dependent formation of endosomes containing water channels, was absent in the cultured cells. These results demonstrate presence of a urea transporter on suspended IMCD cells which is activated by cAMP and inhibited by phloretin and urea analogues. The urea transporter and its regulation by cAMP, and cAMP-dependent apical membrane endocytosis, are lost after growth in primary culture.

CONTROLLED TERM: Check Tags: Female
Animals
Biological Transport
Cells, Cultured
Cyclic AMP: ME, metabolism
Kidney Medulla: CY, cytology
*Kidney Medulla: ME, metabolism
Kinetics
Osmosis
Rats
Rats, Inbred Strains
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
*Urea: ME, metabolism
Vasopressins: PD, pharmacology

CAS REGISTRY NO.: 11000-17-2 (Vasopressins); 57-13-6 (Urea); 60-92-4 (Cyclic

AMP)

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ACCESSION NUMBER: 2003470274 EMBASE
TITLE: Sodium and Chloride Concentrations, pH, and Depth of Airway Surface Liquid in Distal Airways.
AUTHOR: Song Y.; Thiagarajah J.; **Verkman A.S.**
CORPORATE SOURCE: A.S. Verkman, 1246 Health Sciences East Tower, Cardiovascular Research Institute, University of California, San Francisco, CA 94143-0521, United States. verkman@itsa.ucsf.edu
SOURCE: Journal of General Physiology, (2003) Vol. 122, No. 5, pp. 511-519. .
Refs: 28
ISSN: 0022-1295 CODEN: JGPLAD
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20031211
Last Updated on STN: 20031211

ABSTRACT: The composition and depth of the airway surface liquid (ASL) are key parameters in airway physiology that are thought to be important in the pathophysiology of cystic fibrosis and other diseases of the airways. We reported novel fluorescent indicator and microscopy methods to measure [Na (+)], [Cl(-)], pH, and depth of the ASL in large airways (Jayaraman, S., Y. Song, L. Vetrivel, L. Shankar, and A.S. Verkman. 2001. J. Clin. Invest. 107:317-324.). Here we report a stripped-lung preparation to measure ASL composition and depth in small distal airways. Distal ASL was stained with ion- or pH-sensitive fluorescent indicators by infusion into mouse trachea of a perfluorocarbon suspension of the indicator. After stripping the pleura and limited microdissection of the lung parenchyma, airways were exposed for measurement of ASL [Na(+)], [Cl(-)], and pH by ratio imaging microscopy, and depth by confocal microscopy. The stripped-lung preparation was validated in stability and tissue viability studies. ASL [Na(+)] was 122 ± 2 nM, was 123 ± 4 mM and pH was 7.28 ± 0.07, and not dependent on airway size (<100- to >250-μm diameter), ENaC inhibition by amiloride, or CFTR inhibition by the thiazolidinone CFTPr(inh)-172. ASL depth was 8-35 μm depending on airway size, substantially less than that in mouse trachea of .apprx.55 μm, and not altered significantly by amiloride. These results establish a novel lung preparation and fluorescence approach to study distal airway physiology and provide the first data on the composition and depth of distal ASL.

CONTROLLED TERM: Medical Descriptors:
*airway
*pH
*liquid
*airway surface liquid
bronchiole
fluorescence microscopy
chemical composition
cystic fibrosis: ET, etiology
respiratory tract disease: ET, etiology
lung
imaging
ratio imaging
confocal microscopy
sodium channel

chloride channel
nonhuman
mouse
animal tissue
adolescent
article
Drug Descriptors:
*sodium
*chloride
indicator
fluorocarbon
amiloride
2,4 thiazolidinedione

CAS REGISTRY NO.: (sodium) 7440-23-5; (chloride) 16887-00-6; (fluorocarbon) 11072-16-5; (amiloride) 2016-88-8, 2609-46-3; (**2,4 thiazolidinedione**) **2295-31-0**

L136 ANSWER 20 OF 23 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2003246756 EMBASE

TITLE: **CFTR** activation in human bronchial epithelial cells by novel benzoflavone and benzimidazolone compounds.

AUTHOR: Caci E.; Folli C.; Zegarra-Moran O.; **Ma T.**; Springsteel M.F.; Sammelson R.E.; Nantz M.H.; Kurth M.J.; **Verkman A.S.**; Galietta L.J.V.

CORPORATE SOURCE: L.J.V. Galietta, Laboratorio di Genetica Molecolare, Istituto Giannina Gaslini, L.go Gerolamo Gaslini, 5, 16148 Genova, Italy. galietta@unige.it

SOURCE: American Journal of Physiology - Lung Cellular and Molecular Physiology, (1 Jul 2003) Vol. 285, No. 1 29-1, pp. L180-L188. .
Refs: 29
ISSN: 1040-0605 CODEN: APLPE7

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 002 Physiology
029 Clinical Biochemistry
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20030710
Last Updated on STN: 20030710

ABSTRACT: Activators of the **CFTR** Cl(-) channel may be useful for therapy of **cystic** fibrosis. Short-circuit current (I(sc)) measurements were done on human bronchial epithelial cells to characterize the best flavone and benzimidazolone **CFTR** activators identified by lead-based combinatorial synthesis and high-throughput screening. The 7,8-benzoflavone UCCF-029 was a potent activator of Cl(-) transport, with activating potency (<1 μM) being much better than other flavones, such as apigenin. The benzimidazolone UCCF-853 gave similar I(sc) but with lower potency (5-20 μM). In combination, the effect induced by maximal UCCF-029 and UCCF-853 was 50-80% greater than that of either compound alone. The apparent activating potencies (K(d)) of UCCF-029, UCCF-853, and apigenin increased strongly with increasing basal **CFTR** activity: for example, K(d) for activation by UCCF-029 decreased from >5 to <0.4 μM with increasing basal I(sc) from .apprx.4 μA/cm(2) to .apprx.12 μA/cm(2). This dependence was confirmed in permeabilized Fischer rat thyroid cells stably expressing **CFTR**. Our results demonstrate efficacy of novel ***CFTR*** activators in bronchial epithelia and provide evidence that activating potency depends on basal **CFTR** activity.

CONTROLLED TERM: Medical Descriptors:
***cystic fibrosis**
*respiratory epithelium
*chloride transport
signal transduction
concentration response
drug screening
drug potency
human
nonhuman
rat
controlled study
human cell
animal cell
article
priority journal
Drug Descriptors:
*transmembrane conductance regulator: EC, endogenous compound
*benzoflavone derivative: AN, drug analysis
*benzoflavone derivative: CM, drug comparison
*benzoflavone derivative: DV, drug development
*benzoflavone derivative: PD, pharmacology
*benzimidazolone derivative: AN, drug analysis
*benzimidazolone derivative: CM, drug comparison
*benzimidazolone derivative: DV, drug development
*benzimidazolone derivative: PD, pharmacology
*benzimidazole derivative: AN, drug analysis
*benzimidazole derivative: CM, drug comparison
*benzimidazole derivative: DV, drug development
*benzimidazole derivative: PD, pharmacology
chloride ion: EC, endogenous compound
forskolin: CM, drug comparison
forskolin: PD, pharmacology
glibenclamide: CM, drug comparison
glibenclamide: PD, pharmacology
8 (4 chlorophenylthio) cyclic AMP: CM, drug comparison
8 (4 chlorophenylthio) cyclic AMP: PD, pharmacology
apigenin: CM, drug comparison
apigenin: PD, pharmacology
2 (4 pyridyl)benzo[h] 4h chromen 4 one: AN, drug analysis
2 (4 pyridyl)benzo[h] 4h chromen 4 one: CM, drug comparison
2 (4 pyridyl)benzo[h] 4h chromen 4 one: DV, drug development
2 (4 pyridyl)benzo[h] 4h chromen 4 one: PD, pharmacology
1 (3 chlorophenyl) 5 trifluoromethyl 3 hydrobenzamidazol 2 one: AN, drug analysis
1 (3 chlorophenyl) 5 trifluoromethyl 3 hydrobenzamidazol 2 one: CM, drug comparison
1 (3 chlorophenyl) 5 trifluoromethyl 3 hydrobenzamidazol 2 one: DV, drug development
1 (3 chlorophenyl) 5 trifluoromethyl 3 hydrobenzamidazol 2 one: PD, pharmacology
1 (5 chloro 2 hydroxyphenyl) 5 trifluoromethyl 2 benzimidazolone
unclassified drug
uccf 853
uccf 029
CAS REGISTRY NO.: (forskolin) 66575-29-9; (glibenclamide) 10238-21-8; (8 (4

chlorophenylthio) cyclic AMP) 41941-66-6; (apigenin) 520-36-5; (1 (5 chloro 2 hydroxyphenyl) 5 trifluoromethyl 2 benzimidazolone) 141797-92-4
CHEMICAL NAME: Ns 004; Uccf 853; Uccf 029

L136 ANSWER 21 OF 23 USPATFULL on STN
ACCESSION NUMBER: 2005:275177 USPATFULL
TITLE: Hydrazide-containing **CFTR** inhibitor compounds and uses thereof
INVENTOR(S): **Verkman, Alan**, San Francisco, CA, UNITED STATES
Sonawane, Nitin Dattatraya, San Francisco, CA, UNITED STATES
Muanprasat, Chatchai, Nakhonpathom, THAILAND

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005239740	A1	20051027
APPLICATION INFO.:	US 2005-93749	A1	20050329 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2004-557930P	20040330 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BOZICEVIC, FIELD & FRANCIS LLP, 1900 UNIVERSITY AVENUE, SUITE 200, EAST PALO ALTO, CA, 94303, US
NUMBER OF CLAIMS: 55
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 18 Drawing Page(s)
LINE COUNT: 3043
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides compositions, pharmaceutical preparations and methods for inhibition of **cystic fibrosis** transmembrane conductance regulator protein (**CFTR**) that are useful for the study and treatment of **CFTR**-mediated diseases and conditions. The compositions and pharmaceutical preparations of the invention may comprise one or more hydrazide-containing compounds, and may additionally comprise one or more pharmaceutically acceptable carriers, excipients and/or adjuvants. The methods of the invention comprise, in certain embodiments, administering to a patient suffering from a **CFTR**-mediated disease or condition, an efficacious amount of a hydrazide-containing compound. In other embodiments the invention provides methods of inhibiting **CFTR** that comprise contacting cells in a subject with an effective amount of a hydrazide-containing compound. In addition, the invention features a non-human animal model of **CFTR**-mediated disease which model is produced by administration of a hydrazide-containing compound to a non-human animal in an amount sufficient to inhibit **CFTR**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L136 ANSWER 22 OF 23 USPATFULL on STN
ACCESSION NUMBER: 2004:299931 USPATFULL
TITLE: **Cystic fibrosis** transmembrane conductance regulator protein inhibitors and uses thereof

INVENTOR(S): **Verkman, Alan**, San Francisco, CA, UNITED STATES
Ma, Tonghui, San Francisco, CA, UNITED STATES

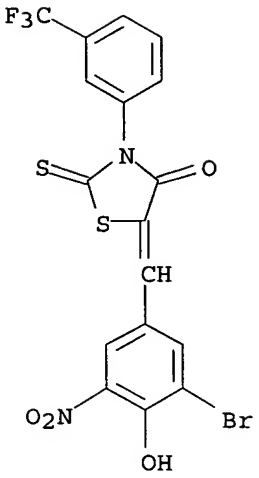
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004235800	A1	20041125
APPLICATION INFO.:	US 2003-676727	A1	20030930 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-509049P	20020930 (60)
	US 2003-480253P	20030620 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BOZICEVIC, FIELD & FRANCIS LLP, 1900 UNIVERSITY AVE, SUITE 200, EAST PALO ALTO, CA, 94303
NUMBER OF CLAIMS: 64
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 2476
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides compositions, pharmaceutical preparations and methods for inhibition of **cystic fibrosis** transmembrane conductance regulator protein (**CFTR**) that are useful for the study and treatment of **CFTR**-mediated diseases and conditions. The compositions and pharmaceutical preparations of the invention may comprise one or more thiazolidinone compounds, and may additionally comprise one or more pharmaceutically acceptable carriers, excipients and/or adjuvants. The methods of the invention comprise, in certain embodiments, administering to a patient suffering from a **CFTR**-mediated disease or condition, an efficacious amount of a thiazolidinone compound. In other embodiments the invention provides methods of inhibiting **CFTR** that comprise contacting cells in a subject with an effective amount of a thiazolidinone compound. In addition, the invention features a non-human animal model of **CFTR**-mediated disease which model is produced by administration of a thiazolidinone compound to a non-human animal in an amount sufficient to inhibit **CFTR**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **292174-08-4**, 3-[(3-Trifluoromethyl)phenyl]-5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone **301308-44-1**, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone **303056-54-4 307510-92-5**, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone **328250-71-1**, 3-[(3-Trifluoromethyl)phenyl]-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone **535962-72-2**, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyoxyphenyl)methylene]-2-thioxo-4-thiazolidinone
(thiazolidinone compound CFTR inhibitors, uses, and animal model of CFTR-mediated disease)
RN 292174-08-4 USPATFULL
CN 4-Thiazolidinone, 5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



RN 301308-44-1 USPATFULL
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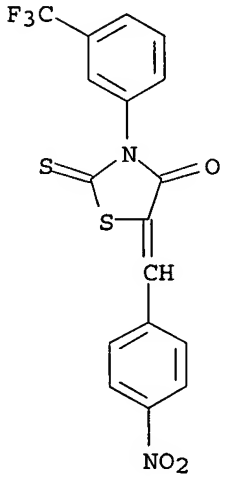

RN 303056-54-4 USPATFULL
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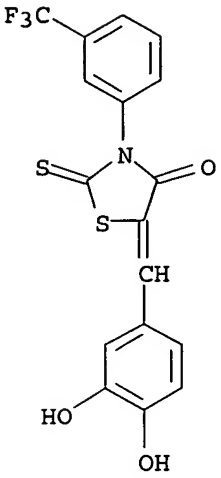
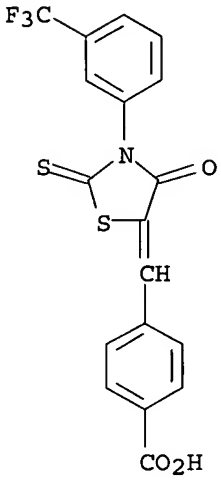
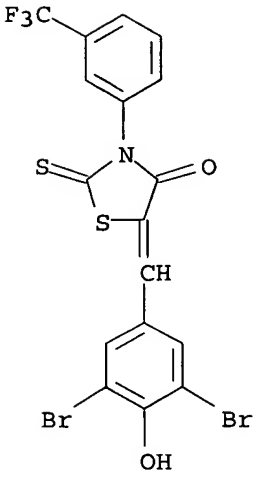


RN 307510-92-5 USPATFULL
CN Benzoic acid, 4-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinylidene]methyl]- (9CI) (CA INDEX NAME)



RN 328250-71-1 USPATFULL
CN 4-Thiazolidinone, 5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



RN 535962-72-2 USPATFULL
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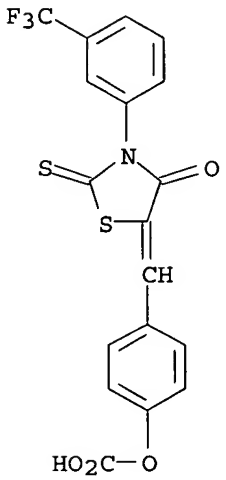
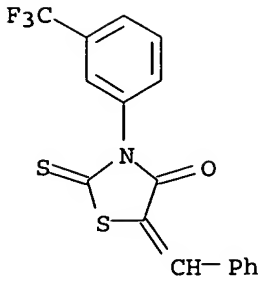
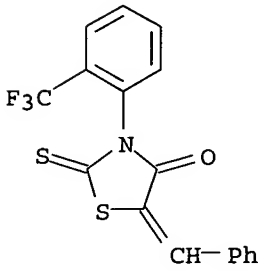


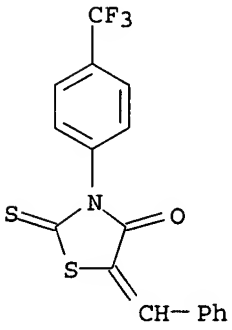
IT **292174-03-9 671247-72-6 671247-73-7**
(thiazolidinone compound CFTR inhibitors, uses, and animal model of CFTR-mediated disease)
RN 292174-03-9 USPATFULL
CN 4-Thiazolidinone, 5-(phenylmethylene)-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



RN 671247-72-6 USPATFULL
CN 4-Thiazolidinone, 5-(phenylmethylene)-2-thioxo-3-[2-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



RN 671247-73-7 USPATFULL
CN 4-Thiazolidinone, 5-(phenylmethylene)-2-thioxo-3-[4-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



L136 ANSWER 23 OF 23 USPATFULL on STN
ACCESSION NUMBER: 2001:36963 USPATFULL
TITLE: Halide indicators
INVENTOR(S): **Verkman, Alan S.**, San Francisco, CA, United States
Biwersi, Joachim, San Francisco, CA, United States
Jayaraman, Sujatha, San Francisco, CA, United States
PATENT ASSIGNEE(S): The Regents of the University of California, Oakland, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6201116	B1	20010313	
APPLICATION INFO.:	US 1999-277354		19990326	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Lee, Howard C.
LEGAL REPRESENTATIVE: Osman, Richard Aron
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
LINE COUNT: 1508
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides methods and compositions for measuring ion concentration inside a cell by measuring fluorescence of a compound of the general formula I. In particular embodiments, the measured ion is halide, particularly iodide, the cell contains a functional anion transport protein or channel, the method measures a change in fluorescence as a function of a predetermined condition such as the presence of a predetermined amount of a candidate modulator of ion transport in the cell (e.g. for drug screening) or the expression by the cell of a transgene (e.g. to assess the efficacy of gene therapy).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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FILE LAST UPDATED: 15 Feb 2006  (20060215/ED)

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L7              STR
L9       101796 SEA FILE=REGISTRY SSS FUL L7
L35             STR
L38           2 SEA FILE=REGISTRY SUB=L9 FAM FUL L35
L39           9 SEA FILE=CAPLUS ABB=ON  PLU=ON  L38

=> d que nos L40

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L14        4392 SEA FILE=CAPLUS ABB=ON  PLU=ON  CFTR?/BI
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L19           1 SEA FILE=CAPLUS ABB=ON  PLU=ON  (?FIBRO CYSTIC?)/BI
L20       11128 SEA FILE=CAPLUS ABB=ON  PLU=ON  (?CYSTIC FIBRO?)/BI
L23       10507 SEA FILE=CAPLUS ABB=ON  PLU=ON  ION TRANSPORT/OBI
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L40           9 SEA FILE=CAPLUS ABB=ON  PLU=ON  L39 AND (L11 OR L12 OR L14 OR
                (L18 OR L19 OR L20) OR L23)

=> s (L39-L40) not L131

L137          3 ((L39 OR L40)) NOT L131
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=> file medline

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 FILE LAST UPDATED: 15 FEB 2006 (20060215/UP).  FILE COVERS 1950 TO DATE.

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 on the 2005 reload, enter HELP RLOAD at an arrow promt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate

=> d que nos L55

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L9       101796 SEA FILE=REGISTRY SSS FUL L7
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L54             SEL  PLU=ON  L38 1- CHEM :        4 TERMS
L55           1 SEA FILE=MEDLINE ABB=ON  PLU=ON  L54


=> s L55 not L132

L138          0 L55 NOT L132

=> file embase

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 FILE COVERS 1974 TO 9 Feb 2006 (20060209/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que nos L85

L7              STR
L9       101796 SEA FILE=REGISTRY SSS FUL L7
L35             STR
L38           2 SEA FILE=REGISTRY SUB=L9 FAM FUL L35
L73       53696 SEA FILE=EMBASE ABB=ON  PLU=ON  CYSTIC?
L74        1353 SEA FILE=EMBASE ABB=ON  PLU=ON  (FIBROCYSTIC? OR (FIBRO
                CYST?))
L75           6 SEA FILE=EMBASE ABB=ON  PLU=ON  MUCOVISCOID?
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printed with author search

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L76          3377 SEA FILE=EMBASE ABB=ON  PLU=ON  CFTR?
L82               SEL  PLU=ON  L38 1- CHEM :        4 TERMS
L83             2 SEA FILE=EMBASE ABB=ON  PLU=ON  L82
L84             2 SEA FILE=EMBASE ABB=ON  PLU=ON  (L38 OR L83 )
L85             2 SEA FILE=EMBASE ABB=ON  PLU=ON  L84 AND ((L73 OR L74 OR L75 OR
                  L76))

=> s L85 not L133

L139            1 L85 NOT L133

=> file biosis

FILE 'BIOSIS' ENTERED AT 12:45:45 ON 16 FEB 2006
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 15 February 2006 (20060215/ED)


=> d que nos L110

L7                STR
L9         101796 SEA FILE=REGISTRY SSS FUL L7
L35               STR
L38             2 SEA FILE=REGISTRY SUB=L9 FAM FUL L35
L108              SEL  PLU=ON  L38 1- CHEM :        4 TERMS
L109            2 SEA FILE=BIOSIS ABB=ON  PLU=ON  L108
L110            2 SEA FILE=BIOSIS ABB=ON  PLU=ON  (L38 OR L109 )

=> s L110 not L134

L140            2 L110 NOT L134

=> file uspatfull

FILE 'USPATFULL' ENTERED AT 12:45:47 ON 16 FEB 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 16 Feb 2006 (20060216/PD)
FILE LAST UPDATED: 16 Feb 2006 (20060216/ED)
HIGHEST GRANTED PATENT NUMBER: US7000250
HIGHEST APPLICATION PUBLICATION NUMBER: US2006037120
CA INDEXING IS CURRENT THROUGH 14 Feb 2006 (20060214/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 16 Feb 2006 (20060216/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2005


=> d que nos L122

L7                STR
L9         101796 SEA FILE=REGISTRY SSS FUL L7
L35               STR
L38             2 SEA FILE=REGISTRY SUB=L9 FAM FUL L35
```

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L112          2 SEA FILE=USPATFULL ABB=ON  PLU=ON  L38
L116      11441 SEA FILE=USPATFULL ABB=ON  PLU=ON  CYSTIC FIBR?
L117       1108 SEA FILE=USPATFULL ABB=ON  PLU=ON  FIBROCYSTIC? OR (FIBRO
                CYSTIC?)
L118       3284 SEA FILE=USPATFULL ABB=ON  PLU=ON  CFTR?
L120            SEL  PLU=ON  L38 1- CHEM :       4 TERMS
L121          3 SEA FILE=USPATFULL ABB=ON  PLU=ON  L120
L122          3 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L112 OR L121) AND (L116 OR
                L117 OR L118)

=> s L122 not L135
L141          1 L122 NOT L135

=> => dup rem L137 L139 L140 L141
FILE 'CAPLUS' ENTERED AT 12:47:01 ON 16 FEB 2006
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE 'USPATFULL' ENTERED AT 12:47:01 ON 16 FEB 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)
PROCESSING COMPLETED FOR L137
PROCESSING COMPLETED FOR L139
PROCESSING COMPLETED FOR L140
PROCESSING COMPLETED FOR L141
L142          5 DUP REM L137 L139 L140 L141 (2 DUPLICATES REMOVED)
                ANSWERS '1-3' FROM FILE CAPLUS
                ANSWER '4' FROM FILE BIOSIS
                ANSWER '5' FROM FILE USPATFULL

=> d ibib abs hitind hitstr L142 1-3; d iall L142 4; d ibib abs kwic hitstr L142 5

L142 ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2006 ACS on STN  DUPLICATE 1
ACCESSION NUMBER:         2004:671764  CAPLUS
DOCUMENT NUMBER:          141:222260
TITLE:                    Effects of a new cystic fibrosis
                          transmembrane conductance regulator inhibitor on Cl-
                          conductance in human sweat ducts
AUTHOR(S):                Wang, X. F.; Reddy, M. M.; Quinton, P. M.
CORPORATE SOURCE:         Department of Pediatrics, University of California San
                          Diego, La Jolla, CA, 92093-0831, USA
SOURCE:                   Experimental Physiology (2004), 89(4), 417-425
                          CODEN: EXPHEZ; ISSN: 0958-0670
PUBLISHER:                Blackwell Publishing Ltd.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB    Effective and specific inhibition of the cystic fibrosis
      transmembrane conductance regulator (CFTR) Cl- channel in
      epithelia has long been needed to better understand the role of anion
      movements in fluid and electrolyte transport.  Until now, available
      inhibitors have required high concns., usually in the millimolar or high
      micromolar range, to effect even an incomplete block of channel
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conductance. These inhibitors, including 5-nitro-2(3-phenylpropyl-amino)benzoate (NPPB), bumetamide, glibenclamide and DIDS, are also relatively non-specific. Recently a new anion channel inhibitor, a thiazolidinone derivative, termed **CFTRInh**-172 has been synthesized and introduced with apparently improved inhibitory properties as shown by effects on anion conductance expressed in cell lines and on secretion in vivo. Here, we assay the effect of this inhibitor on a purely salt absorbing native epithelial tissue, the freshly isolated microperfused human sweat duct, known for its inherently high expression of **CFTR** . We found that the inhibitor at a maximum dose limited by its aqueous solubility of 5 μm partially blocked **CFTR** when applied to either surface of the membrane; however, it may be somewhat more effective from the cytosolic side (.apprx.70% inhibition). It may also partially inhibit Na+ conductance. The inhibition was relatively slow, with a half time for maximum effect of about 3 min, and showed very slow reversibility. Results also suggest that **CFTR** Cl- conductance (GCl) was blocked in both apical and basal membranes. The inhibitor appears to exert some effect on Na+ transport as well.

CC 13-2 (Mammalian Biochemistry)
Section cross-reference(s): 6

ST **CFTR** inhibitor **CFTRInh172** chloride conductance sweat duct

IT Biological transport
(chloride; effects of new **cystic fibrosis** transmembrane conductance regulator inhibitor on Cl- conductance in human sweat ducts)

IT Sweat gland
(duct; effects of new **cystic fibrosis** transmembrane conductance regulator inhibitor on Cl- conductance in human sweat ducts)

IT Human
(effects of new **cystic fibrosis** transmembrane conductance regulator inhibitor on Cl- conductance in human sweat ducts)

IT **CFTR** (**cystic fibrosis** transmembrane conductance regulator)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(effects of new **cystic fibrosis** transmembrane conductance regulator inhibitor on Cl- conductance in human sweat ducts)

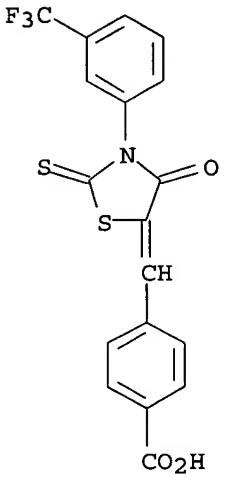
IT Biological transport
(sodium; effects of new **cystic fibrosis** transmembrane conductance regulator inhibitor on Cl- and Na+ transport in human sweat ducts)

IT **307510-92-5**, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**CFTRInh**-172; effects of new **cystic fibrosis** transmembrane conductance regulator inhibitor on Cl- conductance in human sweat ducts)

IT 7440-23-5, Sodium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(transport; effects of new **cystic fibrosis** transmembrane conductance regulator inhibitor on Cl- and Na+ transport in human sweat ducts)

IT 16887-00-6, Chloride, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(transport; effects of new **cystic fibrosis** transmembrane conductance regulator inhibitor on Cl- conductance in

human sweat ducts)
IT **307510-92-5**, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**CFTRInh**-172; effects of new **cystic fibrosis** transmembrane conductance regulator inhibitor on Cl- conductance in human sweat ducts)
RN 307510-92-5 CAPLUS
CN Benzoic acid, 4-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinylidene]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L142 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1134223 CAPLUS
DOCUMENT NUMBER: 144:396
TITLE: A novel small molecule **CFTR** inhibitor attenuates HCO3- secretion and duodenal ulcer formation in rats
AUTHOR(S): Akiba, Yasutada; Jung, Michael; Ouk, Samedy; Kaunitz, Jonathan D.
CORPORATE SOURCE: Department of Medicine, School of Medicine, University of California, Los Angeles, CA, USA
SOURCE: American Journal of Physiology (2005), 289(4, Pt. 1), G753-G759
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **cystic fibrosis** (CF) transmembrane conductance regulator (**CFTR**) plays a crucial role in mediating duodenal bicarbonate (HCO3-) secretion (DBS). Although impaired DBS is observed in CF mutant mice and in CF patients, which would predict increased ulcer susceptibility, duodenal injury is rarely observed in CF patients and is reduced in CF mutant mice. To explain this apparent paradox, we hypothesized that **CFTR** dysfunction increases cellular [HCO3-] and buffering power. To further test this hypothesis, we examined the effect of a novel, potent, and highly selective **CFTR** inhibitor, **CFTRinh**-172, on DBS and duodenal ulceration in rats. DBS was

measured in situ using a standard loop perfusion model with a pH stat under isoflurane anesthesia. Duodenal ulcers were induced in rats by cysteamine with or without **CFTRinh**-172 pretreatment 1 h before cysteamine. Superfusion of **CFTRinh**-172 (0.1-10 μM) over the duodenal mucosa had no effect on basal DBS but at 10 μM inhibited acid-induced DBS, suggesting that its effect was limited to **CFTR** activation. Acid-induced DBS was abolished at 1 and 3 h and was reduced 24 h after treatment with **CFTRinh**-172, although basal DBS was increased at 24 h. **CFTRinh**-172 treatment had no effect on gastric acid or HCO3- secretion. Duodenal ulcers were observed 24 h after cysteamine treatment but were reduced in **CFTRinh**-172-pretreated rats. **CFTRinh**-172 acutely produces **CFTR** dysfunction in rodents for up to 24 h. **CFTR** inhibition reduces acid-induced DBS but also prevents duodenal ulcer formation, supporting our hypothesis that intracellular HCO3- may be an important protective mechanism for duodenal epithelial cells.

CC 1-9 (Pharmacology)
Section cross-reference(s): 13, 14

ST thiazolidinone **CFTRinh172** **CFTR** inhibitor bicarbonate secretion duodenal ulcer

IT Epithelium
Ulcer
(duodenal; novel small mol. **CFTR** inhibitor attenuates bicarbonate secretion and duodenal ulcer formation in rats)

IT Intestine
(duodenum, epithelium; novel small mol. **CFTR** inhibitor attenuates bicarbonate secretion and duodenal ulcer formation in rats)

IT Intestine, disease
(duodenum, ulcer; novel small mol. **CFTR** inhibitor attenuates bicarbonate secretion and duodenal ulcer formation in rats)

IT Secretion (process)
(novel small mol. **CFTR** inhibitor attenuates bicarbonate secretion and duodenal ulcer formation in rats)

IT **CFTR** (**cystic fibrosis** transmembrane conductance regulator)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(novel small mol. **CFTR** inhibitor attenuates bicarbonate secretion and duodenal ulcer formation in rats)

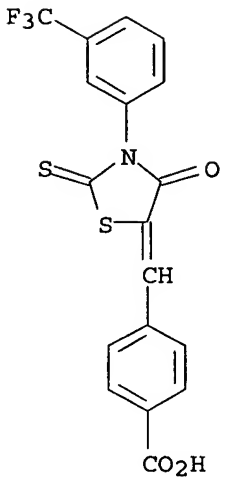
IT **307510-92-5**, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**CFTRh**-172; novel small mol. **CFTR** inhibitor attenuates bicarbonate secretion and duodenal ulcer formation in rats)

IT 71-52-3, Bicarbonate, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(novel small mol. **CFTR** inhibitor attenuates bicarbonate secretion and duodenal ulcer formation in rats)

IT **307510-92-5**, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**CFTRh**-172; novel small mol. **CFTR** inhibitor attenuates bicarbonate secretion and duodenal ulcer formation in rats)

RN 307510-92-5 CAPLUS

CN Benzoic acid, 4-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinylidene]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L142 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:108287 CAPLUS
DOCUMENT NUMBER: 143:191261
TITLE: Predominant constitutive **CFTR** conductance in small airways
AUTHOR(S): Wang, Xiaofei; Lytle, Christian; Quinton, Paul M.
CORPORATE SOURCE: Dept. Prediatrics, Med. Sch., Univ. California, San Diego, San Diego, CA, USA
SOURCE: Respiratory Research (2005), 6(1), No pp. given
CODEN: RREEBZ; ISSN: 1465-993X
URL: http://respiratory-research.com/content/pdf/1465-9921-6-7.pdf
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB Background: The pathol. hallmarks of chronic obstructive pulmonary disease (COPD) are inflammation of the small airways (bronchiolitis) and destruction of lung parenchyma (emphysema). These forms of disease arise from chronic prolonged infections, which are usually never present in the normal lung. Despite the fact that primary hygiene and defense of the airways presumably requires a well controlled fluid environment on the surface of the bronchiolar airway, very little is know of the fluid and electrolyte transport properties of airways of less than a few mm diameter Methods: We introduce a novel approach to examine some of these properties in a preparation of minimally traumatized porcine bronchioles of about 1 mm diameter by microperfusing the intact bronchiole. Results: In bilateral isotonic NaCl Ringer solns., the spontaneous transepithelial potential (TEP; lumen to bath) of the bronchiole was small (mean+sem: -3± mV; n=25), but when gluconate replaced luminal Cl- the bionic Cl- diffusion potentials (-58±3 mV; n=25) were as large as -90 mV. TEP diffusion potentials from 2:1 NaCl dilution showed that epithelial Cl- permeability was at least 5 times greater than Na+ permeability. The anion selectivity sequence was similar to that of **CFTR**. The bionic TEP became more electroneg. with stimulation by luminal forskolin (5 μM)+IBMX (100 μM), ATP (100 μM), or adenosine (100 μM), but not by ionomycin. The TEP was partially inhibited by NPPB (100 μM), GlyH-101* (5-50 μM), and **CFTRInh**-172* (5 μM). RT-PCR gave identifying

products for **CFTR**, α-, β-, and γ-ENaC and NKCC1. Antibodies to **CFTR** localized specifically to the epithelial cells lining the lumen of the small airways. Conclusion: These results indicate that the small airway of the pig is characterized by a constitutively active Cl- conductance that is most likely due to **CFTR**.

CC 14-4 (Mammalian Pathological Biochemistry)

ST gluconate amiloride forskolin IBMX **cystic fibrosis** transmembrane conductance regulator

IT Sodium channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SCNN1A; predominant constitutive **CFTR** conductance in small airways)

IT Sodium channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SCNN1B; predominant constitutive **CFTR** conductance in small airways)

IT Sodium channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SCNN1G; predominant constitutive **CFTR** conductance in small airways)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ZO-1 (zonula occludens 1); predominant constitutive **CFTR** conductance in small airways)

IT Drug targets
(anion conductance inhibitor NPPB, GlyH-101 and **CFTRInh**-172 significantly depolarized transepithelial potential in pig bronchiole)

IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(chloride-potassium-sodium cotransporter SLC12A2; predominant constitutive **CFTR** conductance in small airways)

IT Lung, disease
(chronic obstructive pulmonary disease; predominant constitutive **CFTR** conductance in small airways)

IT **CFTR** (**cystic fibrosis** transmembrane conductance regulator)
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(constitutively active chloride ion conductance was found in partially traumatized pig small bronchioles suggesting activation of **cystic fibrosis** transmembrane conductance regulator)

IT Respiratory system
(predominant constitutive **CFTR** conductance in small airways)

IT **307510-92-5**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(anion conductance inhibitor **CFTRInh**-172 significantly depolarized transepithelial potential in pig bronchiole)

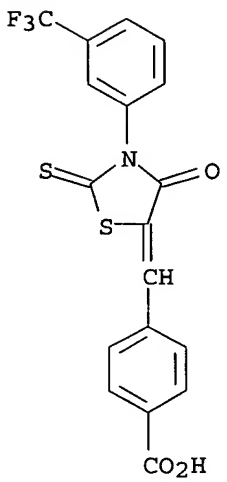
IT 16887-00-6, Chloride ion, biological studies
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(constitutively active chloride ion conductance was found in partially traumatized pig small bronchioles suggesting activation of **cystic fibrosis** transmembrane conductance regulator)

IT **307510-92-5**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(anion conductance inhibitor **CFTRInh**-172 significantly depolarized transepithelial potential in pig bronchiole)

RN 307510-92-5 CAPLUS

CN Benzoic acid, 4-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-

thiazolidinylidene]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L142 ANSWER 4 OF 5 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:139004 BIOSIS
DOCUMENT NUMBER: PREV200500137365
TITLE: In vivo pharmacology and antidiarrheal efficacy of a thiazolidone CFTR inhibitor in rodents.
AUTHOR(S): Sonawane, N. D.; Muanprasat, Chatchai; Nagatani, Ray Jr; Song, Yuanlin; Verkman, A. S. [Reprint Author]
CORPORATE SOURCE: Cardiovasc Res InstDept Med, Univ Calif San Francisco, San Francisco, CA, 94143, USA
verkman@itsa.ucsf.edu
SOURCE: Journal of Pharmaceutical Sciences, (January 2005) Vol. 94, No. 1, pp. 134-143. print.
CODEN: JPMSAE. ISSN: 0022-3549.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Apr 2005
Last Updated on STN: 6 Apr 2005

ABSTRACT:A small-molecule inhibitor of the cystic fibrosis transmembrane conductance regulator (CFTR), **3-((3-trifluoromethyl)phenyl)-5-((4-carboxyphenyl) ***methylene***)-2-thioxo-4- ***thiazolidinone*** (CFTRinh-172), reduces enterotoxin-induced intestinal fluid secretion in rodents. Here, we study CFTRinh-172 pharmacology and antidiarrheal efficacy in rodents using14 C-labeled CFTRinh-172, liquid chromatography/mass spectrometry, and a closed intestinal loop model of fluid secretion. CFTRinh-172 was cleared primarily by renal glomerular filtration without chemical modification. CFTRinh-172 accumulated in liver within 5 min after intravenous infusion in mice, and was concentrated fivefold in bile over blood. At 30-240 min, CFTRinh-172 was found mainly in liver, intestine, and kidney, with little detectable in the brain, heart, skeletal muscle, or lung. Pharmacokinetic analysis in rats following intravenous bolus infusion showed a distribution volume of 770 mL with redistribution and elimination half-times of

0.14 h and 10.3 h, respectively. CFTRinh-172 was stable in hepatic microsomes. Closed-loop studies in mice indicated that a single intraperitoneal injection of 20 mug CFTRinh-172 inhibited fluid accumulation at 6 h after cholera toxin by >90% in duodenum and jejunum, apprx60% in ileum and <10% in colon. No toxicity was seen after high-dose CFTRinh-172 administration (3 mg/kg/day in two daily doses) in mice over the first 6 weeks of life. The metabolic stability, enterohepatic recirculation, slow renal elimination, and intestinal accumulation of CFTRinh-172 account for its efficacy as an antidiarrheal.

CONCEPT CODE:
Pathology - Therapy 12512
Digestive system - Physiology and biochemistry 14004
Digestive system - Pathology 14006
Cardiovascular system - Physiology and biochemistry 14504
Urinary system - Physiology and biochemistry 15504
Respiratory system - Physiology and biochemistry 16004
Muscle - Physiology and biochemistry 17504
Nervous system - Physiology and biochemistry 20504
Pharmacology - General 22002
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Digestive system 22014

INDEX TERMS:
Major Concepts
Digestive System (Ingestion and Assimilation); Pharmacology

INDEX TERMS:
Parts, Structures, & Systems of Organisms
brain: nervous system; colon: digestive system; duodenum: digestive system; heart: circulatory system; ileum: digestive system; intestinal fluid: digestive system; intestine: digestive system; jejunum: digestive system; kidney: excretory system; liver: digestive system; lung: respiratory system; microsome; skeletal muscle: muscular system

INDEX TERMS:
Diseases
diarrhea: digestive system disease
Diarrhea (MeSH)

INDEX TERMS:
Chemicals & Biochemicals
3-[(3-trifluoromethyl) phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone [CFTR-inh-172]: antidiarrheal-drug, gastrointestinal-drug, intraperitoneal administration, intravenous administration, pharmacokinetics; cholera toxin; enterotoxin

INDEX TERMS:
Methods & Equipment
liquid chromatography/mass spectrometry: chromatographic techniques, laboratory techniques, spectrum analysis techniques

INDEX TERMS:
Miscellaneous Descriptors
drug metabolism; enterohepatic recirculation; intestinal accumulation; metabolic stability; renal elimination

ORGANISM:
Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Sprague-Dawley rat (common): male
mouse (common): strain-CD1
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates,

L142 ANSWER 5 OF 5 USPATFULL on STN

ACCESSION NUMBER:	2004:300010 USPATFULL		
TITLE:	Method for treatment of chemotherapy-induced diarrhea		
INVENTOR(S):	Ware, Joseph A., Kalamazoo, MI, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004235879	A1	20041125
APPLICATION INFO.:	US 2004-850070	A1	20040520 (10)
	NUMBER		DATE
PRIORITY INFORMATION:	US 2003-472348P		20030521 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Patrick G. Gattari, McDonnell Boehnen Hulbert & Berghoff LLP, 32nd Floor, 300 S. Wacker Drive, Chicago, IL, 60606		
NUMBER OF CLAIMS:	12		
EXEMPLARY CLAIM:	1		
LINE COUNT:	324		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a method for treating diarrhea caused by the interaction of a chemotherapeutic agent with a **CFTR** protein, which comprises administering sequentially, separately or simultaneously with said chemotherapeutic agent a therapeutically effective amount of a **CFTR** protein inhibitor to a patient in need of the treatment of such a diarrhea and a method for optimizing time and dosages of a diarrheagenic chemotherapeutic agent in a patient in need thereof, which comprises evaluating the sensitivity of said patients towards said agent through the detection of chloride levels in a biological sample of said patient and selecting a time and dosages of said agent based on the above chloride levels.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a method for treating diarrhea caused by the interaction of a chemotherapeutic agent with a **CFTR** protein, which comprises administering sequentially, separately or simultaneously with said chemotherapeutic agent a therapeutically effective amount of a **CFTR** protein inhibitor to a patient in need of the treatment of such a diarrhea and a method for optimizing time. . .

DETD [0010] Several studies suggest that **cystic fibrosis** transmembrane conductance regulator (**CFTR**), a member of the ATP-binding Cassette (ABC), subfamily C member 7 (ABCC7) is the final common pathway for intestinal chloride (Cl.sup.-) and thus fluid secretion into the lumen of the small and large intestine. Activation of **CFTR** (ABCC7) by pathogenic microorganisms is a major factor in enterotoxin-induced diarrhea (EID) produced by many gut pathogens. In many examples, second messengers generated in response to an enterotoxin exposure have been shown to activate **CFTR** and thus Cl.sup.- secretion. These second messengers include cAMP and cGMP protein kinase C, inflammatory mediators (such as tumor necrosis. . . arachidonic acid (such as PGE.sub.2). Despite the complex nature of events leading to ultimate effect of EID, the role of **CFTR** has been

established using in-vitro studies and in mice where **CFTR** has been selectively deleted from the mouse.

DETD . . . that camptothecin derivatives, especially irinotecan and its active metabolite SN-38 would produce disturbances in colonic electrolyte transport by interacting with **CFTR** (ABCC7) in the colonic crypts, so contributing to diarrhea associated with the administration of said drug in a manner analogue. . .

DETD [0017] As an example, to determine the interaction of CPT-11, SN-38, and topotecan with **CFTR** (ABCC7), the effect of said substances on Cl.sup.- conductance in **CFTR** (ABCC7)-transfected Xenopus laevis oocytes is evaluated via single voltage clamp conditions.

DETD . . . object of the present invention a method for treating diarrhea caused by the interaction of a chemotherapeutic agent with a **CFTR** protein, which comprises administering sequentially, separately or simultaneously with said chemotherapeutic agent a therapeutically effective amount of a **CFTR** protein inhibitor to a patient in need of the treatment of such a diarrhea.

DETD . . . for treating a cancer sensitive to a potential diarrheagenic chemotherapeutic agent, which comprises administering a therapeutically effective amount of a **CFTR** protein inhibitor for treating diarrhea occurring when said chemotherapeutic agent is administered to a patient.

DETD [0022] According to the present invention, the term "**CFTR** inhibitor" includes small molecules such as glyburide (glibenclamide), thiazolidinones such as for example **3-[(3-trifluoromethyl)phenyl[-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone**, flavinoids and/or monoclonal or polyclonal antibodies directed toward some part of **CFTR** (ABCC7).

DETD . . . from the interaction of a camptothecin derivative, particularly selected from the group consisting of irinotecan, SN-38 and topotecan, with a **CFTR** protein, which comprises administering sequentially, separately or simultaneously with said chemotherapeutic agent a therapeutically effective amount of a **CFTR** protein inhibitor to a patient in need of the treatment of such a diarrhea.

DETD . . . the present invention provides a method for treating diarrhea which results from the interaction of irinotecan or SN-38, with a **CFTR** protein, which comprises administering sequentially, separately or simultaneously with said chemotherapeutic agent a therapeutically effective amount of a **CFTR** protein inhibitor to a patient in need of the treatment of such a diarrhea.

DETD [0026] As an example, the efficacy of a **CFTR** inhibitor for the treatment of diarrhea induced by the administration of a chemotherapeutic agent, such as for example irinotecan or SN-38, may be evaluated in **CFTR** knockout mice.

DETD [0027] It is believed that the subject **CFTR** inhibitor would be found to be effective in the treatment of diarrhea induced by the administration of the selected diarrheagenic. . .

CLM What is claimed is:

1. A method for treating diarrhea caused by the interaction of a diarrheagenic chemotherapeutic agent with a **CFTR** protein, which comprises administering sequentially, separately or simultaneously with said chemotherapeutic agent a therapeutically effective amount of a **CFTR** protein inhibitor to a patient in need of the treatment of such a diarrhea.

. . . for treating a cancer sensitive to a potential diarrheagenic chemotherapeutic agent, which comprises administering a therapeutically effective amount of a **CFTR** protein inhibitor for treating

diarrhea occurring when said chemotherapeutic agent is administered to a patient.

BROADER STRUCTURE/TEXT SEARCH

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=> => file caplus
FILE 'CAPLUS' ENTERED AT 12:54:29 ON 16 FEB 2006
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FILE COVERS 1907 - 16 Feb 2006  VOL 144 ISS 8
FILE LAST UPDATED: 15 Feb 2006  (20060215/ED)

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http://www.cas.org/infopolicy.html
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE

=> d que nos L13

L7              STR
L9       101796 SEA FILE=REGISTRY SSS FUL L7
L10       11681 SEA FILE=CAPLUS ABB=ON  PLU=ON  L9
L11       10928 SEA FILE=CAPLUS ABB=ON  PLU=ON  CYSTIC?/OBI
L13          23 SEA FILE=CAPLUS ABB=ON  PLU=ON  L11 AND L10


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L14        4392 SEA FILE=CAPLUS ABB=ON  PLU=ON  CFTR?/BI
L15          13 SEA FILE=CAPLUS ABB=ON  PLU=ON  L14 AND L10


=> d que nos L22

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L19           1 SEA FILE=CAPLUS ABB=ON  PLU=ON  (?FIBRO CYSTIC?)/BI
L20       11128 SEA FILE=CAPLUS ABB=ON  PLU=ON  (?CYSTIC FIBRO?)/BI
L21       11128 SEA FILE=CAPLUS ABB=ON  PLU=ON  (L19 OR L20)
L22          23 SEA FILE=CAPLUS ABB=ON  PLU=ON  L21 AND L10
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L24              2 SEA FILE=CAPLUS ABB=ON  PLU=ON  L10 AND L23

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L25          62389 SEA FILE=CAPLUS ABB=ON  PLU=ON  ((ION? OR CHLOR?) (3A)
                   ?TRANSP?)/BI
L56             STR
L58           7067 SEA FILE=REGISTRY SUB=L9 SSS FUL L56
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L66              6 SEA FILE=CAPLUS ABB=ON  PLU=ON  L25 AND L59

=> s (L13 or L15 or L22 or L24 or L66) not (L137 or L131)
L143            15 (L13 OR L15 OR L22 OR L24 OR L66) NOT (L137 OR L131)

=> file medline
FILE 'MEDLINE' ENTERED AT 12:54:34 ON 16 FEB 2006

 FILE LAST UPDATED: 15 FEB 2006 (20060215/UP). FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 will soon be available. For details
 on the 2005 reload, enter HELP RLOAD at an arrow promt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate

=> d que nos L60

L7              STR
L9          101796 SEA FILE=REGISTRY SSS FUL L7
L56             STR
L58           7067 SEA FILE=REGISTRY SUB=L9 SSS FUL L56
L60              0 SEA FILE=REGISTRY ABB=ON  PLU=ON  L58 AND MEDLINE/LC

=> d que nos L65
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printed with narrow search

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L7              STR
L9       101796 SEA FILE=REGISTRY SSS FUL L7
L61          29 SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND MEDLINE/LC
L62        3293 SEA FILE=MEDLINE ABB=ON  PLU=ON  L61
L64       14298 SEA FILE=MEDLINE ABB=ON  PLU=ON  ION? (3A) ?TRANSP?
L65           5 SEA FILE=MEDLINE ABB=ON  PLU=ON  L62 AND L64,


=> d que nos L69

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L44        25743 SEA FILE=MEDLINE ABB=ON  PLU=ON  CYSTIC FIBR?
L45         3738 SEA FILE=MEDLINE ABB=ON  PLU=ON  CFTR
L46         3396 SEA FILE=MEDLINE ABB=ON  PLU=ON  FIBROCYST? OR (FIBRO CYST?)
L47         3752 SEA FILE=MEDLINE ABB=ON  PLU=ON  CFTR?
L61           29 SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND MEDLINE/LC
L67              SEL  PLU=ON  L61 1- CHEM :     132 TERMS
L68         6472 SEA FILE=MEDLINE ABB=ON  PLU=ON  L67
L69           16 SEA FILE=MEDLINE ABB=ON  PLU=ON  L68 AND (L44 OR L45 OR L46 OR
                 L47)


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            0 L60
L144       15 (L60 OR L65 OR L69) NOT (L132 OR L138)

=> file embase

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 EMBASE has been reloaded. Enter HELP RLOAD for details.

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=> d que nos L86

L7              STR
L9       101796 SEA FILE=REGISTRY SSS FUL L7
L73        53696 SEA FILE=EMBASE ABB=ON  PLU=ON  CYSTIC?
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                 CYST?))
L75            6 SEA FILE=EMBASE ABB=ON  PLU=ON  MUCOVISCOID?
L76         3377 SEA FILE=EMBASE ABB=ON  PLU=ON  CFTR?
L78           22 SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 AND EMBASE/LC
L79              SEL  PLU=ON  L78 1- CHEM :     110 TERMS
L80         8516 SEA FILE=EMBASE ABB=ON  PLU=ON  L79
L81         8516 SEA FILE=EMBASE ABB=ON  PLU=ON  (L78 OR L80 )
L86           32 SEA FILE=EMBASE ABB=ON  PLU=ON  L81 AND (L73 OR L74 OR L75 OR
                 L76)


=> s L86 not (L133 or L139)

L145       26 L86 NOT (L133 OR L139)
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=> file biosis

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=> d que nos L100

L7                STR
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L95            4798 SEA FILE=BIOSIS ABB=ON  PLU=ON  L94
L96           47945 SEA FILE=BIOSIS ABB=ON  PLU=ON  CYSTIC?
L97            1202 SEA FILE=BIOSIS ABB=ON  PLU=ON  FIBROCYST? OR (FIBRO CYST?)
L98            4750 SEA FILE=BIOSIS ABB=ON  PLU=ON  CFTR
L99            4793 SEA FILE=BIOSIS ABB=ON  PLU=ON  CFTR?
L100              1 SEA FILE=BIOSIS ABB=ON  PLU=ON  L95 AND (L96 OR L97 OR L98 OR
                    L99)


=> d que nos L106

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L96           47945 SEA FILE=BIOSIS ABB=ON  PLU=ON  CYSTIC?
L97            1202 SEA FILE=BIOSIS ABB=ON  PLU=ON  FIBROCYST? OR (FIBRO CYST?)
L98            4750 SEA FILE=BIOSIS ABB=ON  PLU=ON  CFTR
L99            4793 SEA FILE=BIOSIS ABB=ON  PLU=ON  CFTR?
L104                SEL  PLU=ON  L94 1- CHEM :      237 TERMS
L105           6185 SEA FILE=BIOSIS ABB=ON  PLU=ON  L104
L106              6 SEA FILE=BIOSIS ABB=ON  PLU=ON  L105 AND (L96 OR L97 OR L98 OR
                    L99)


=> s (L100 or L106) not (L134 or L140)

L146              3 (L100 OR L106) NOT (L134 OR L140)

=> file uspatfull

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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 16 Feb 2006 (20060216/PD)
FILE LAST UPDATED: 16 Feb 2006 (20060216/ED)
HIGHEST GRANTED PATENT NUMBER: US7000250
HIGHEST APPLICATION PUBLICATION NUMBER: US2006037120
CA INDEXING IS CURRENT THROUGH 14 Feb 2006 (20060214/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 16 Feb 2006 (20060216/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2005
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L56             STR
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L116      11441 SEA FILE=USPATFULL ABB=ON  PLU=ON  CYSTIC FIBR?
L117       1108 SEA FILE=USPATFULL ABB=ON  PLU=ON  FIBROCYSTIC? OR (FIBRO
                CYSTIC?)
L118       3284 SEA FILE=USPATFULL ABB=ON  PLU=ON  CFTR?
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L118       3284 SEA FILE=USPATFULL ABB=ON  PLU=ON  CFTR?
L123            SEL  PLU=ON  L114 1- CHEM :       59 TERMS
L124          4 SEA FILE=USPATFULL ABB=ON  PLU=ON  L123
L125          4 SEA FILE=USPATFULL ABB=ON  PLU=ON  L124 AND (L116 OR L117 OR
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=> s (L119 or L125) not (L141 or L135)

L147          2 (L119 OR L125) NOT (L141 OR L135)
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PROCESSING COMPLETED FOR L144
PROCESSING COMPLETED FOR L145
PROCESSING COMPLETED FOR L146
PROCESSING COMPLETED FOR L147
L148          56 DUP REM L143 L144 L145 L146 L147 (5 DUPLICATES REMOVED)
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ANSWERS '1-15' FROM FILE CAPLUS
ANSWERS '16-29' FROM FILE MEDLINE
ANSWERS '30-53' FROM FILE EMBASE
ANSWER '54' FROM FILE BIOSIS
ANSWERS '55-56' FROM FILE USPATFULL

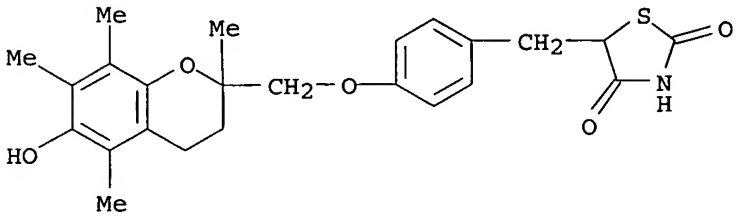
=> d ibib abs hitind hitstr L148 1-15; d iall L148 16-54; d ibib abs kwic hitstr L148 55-56

L148 ANSWER 1 OF 56 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 1999:547926 CAPLUS
DOCUMENT NUMBER: 131:281342
TITLE: Troglitazone inhibits bicarbonate secretion in rat and human duodenum
AUTHOR(S): Hosokawa, M.; Tsukada, H.; Fukuda, K.; Oya, M.; Onomura, M.; Nakamura, H.; Kodama, M.; Yamada, Y.; Seino, Y.
CORPORATE SOURCE: Department of Metabolism and Clinical Nutrition, Faculty of Medicine, Kyoto University, Kyoto, Japan
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1999), 290(3), 1080-1084
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Troglitazone is a new, orally effective antidiabetic agent that decreases plasma glucose in obese patients with non-insulin-dependent diabetes mellitus. Unfortunately, troglitazone also has a propensity to cause edema. This study was designed to determine how troglitazone affects intestinal ion transport and water absorption. Short circuit current (ISC) was measured in rat and human duodenal mucosa in Ussing chambers. Five minutes later, the serosal addition of troglitazone caused ISC to decrease gradually, and after 50 min, ISC reached the peak of decrease. EC50 values and maximum response to ISC in rat and human mucosa were 8.4 and 8.7 μM and 8.56 ± 1.0 and 8.00 ± 2.0 μA/cm2, resp. In an HCO3-/CO2-free system, the decrease in ISC caused by troglitazone was 1.31 ± 0.83 μA/cm2. When 10 mM acetazolamide was preadministered, the small decrease in ISC evoked by troglitazone (20 μM) was 4.56 ± 0.22 μA/cm2, whereas the preadministration of 100 μM amiloride and 100 nM tetrodotoxin did not influence the decrease in ISC evoked by troglitazone. The serosal preadministration of 100 nM vasoactive intestinal peptide potently enhanced the decrease in ISC evoked by 20 μM troglitazone (21.1 ± 1.63 μA/cm2). The cAMP contents of rat duodenal mucosa incubated with and without troglitazone (20 μM) for 50 min were 3.2 ± 0.25 and 5.8 ± 0.46 pmol/mg protein, resp. ($P < 0.01$). These results indicate that the ionic basis for the decrease in ISC that is induced by troglitazone may be inhibition of electrogenic bicarbonate secretion. The alteration of intestinal ion transport by troglitazone could cause edema.
CC 1-10 (Pharmacology)
ST troglitazone intestinal **ion transport** water absorption; bicarbonate secretion duodenum antidiabetic troglitazone
IT **97322-87-7**, Troglitazone
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(troglitazone inhibits bicarbonate secretion in rat and human duodenum)
IT **97322-87-7**, Troglitazone
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or

effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(troglitazone inhibits bicarbonate secretion in rat and human duodenum)

RN 97322-87-7 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L148 ANSWER 2 OF 56 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1289898 CAPLUS

DOCUMENT NUMBER: 144:36334

TITLE: Preparation of phenyl benzoyl pyrazoles as CRTH2 receptor ligands

INVENTOR(S): Ulven, Trond; Frimurer, Thomas; Rist, Oeystein; Kostenis, Evi; Hoegberg, Thomas; Receveur, Jean-Marie; Grimstrup, Marie

PATENT ASSIGNEE(S): 7TM Pharma A/S, Den.

SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

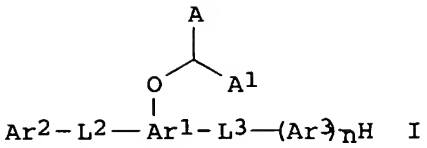
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005115382	A1	20051208	WO 2005-EP5884	20050530

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:		
GB 2004-12198	A	20040529
GB 2004-14196	A	20040624
GB 2004-24018	A	20041029

GI



AB Title compds. I [A = carboxy, carboxy bioisostere; A1 = H, Me; Ar1 = (un)substituted heteroaryl in which the groups OCHAA1 and L2 are linked to adjacent ring atoms; Ar2-3 = heteroaryl; n = 0-1; L2-3 = divalent radical (Alk1)m-Zq-(Alk2)p; m, q, p = 0-1; Alk1-2 = alkylene which may be heteroatom substituted, etc.; Z = O, S, CO SO2, etc.; with some provisions] are prepared For instance, 4-bromo-2-((1-phenyl-1H-pyrazole-4-yl)carbonyl)phenoxyacetic acid (II) is prepared in 2 steps from (5-bromo-2-hydroxyphenyl)(1-phenyl-1H-pyrazol-4-yl)methanone and Et bromoacetate. II has an IC50 < 0.5 μM for the CRTH2 receptor. I are useful for the treatment of disease responsive to modulation of CRTH2 receptor activity, such as asthma, rhinitis, allergic airway syndrome, and allergic rhinobronchitis.

IC ICM A61K031-415
ICS A61K031-454; A61P029-00; A61P043-00

CC 28-8 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

IT Allergy
Allergy inhibitors
Alzheimer's disease
Anti-Alzheimer's agents
Anti-inflammatory agents
Antiarthritics
Antiasthmatics
Antidiabetic agents
Antimigraine agents
Antirheumatic agents
Asthma
Atherosclerosis
Autoimmune disease
Behcet's syndrome
Cardiovascular agents
Central nervous system agents
Cough
Cystic fibrosis
Dermatomyositis
Diabetes insipidus
Diabetes mellitus
Ehlers-Danlos syndrome
Encephalitis
Encephalomyelitis
Gout
Human
Inflammation
Lupus erythematosus
Multiple sclerosis
Myositis
Osteoarthritis
Respiratory system, disease
Rheumatoid arthritis
Sarcoidosis
Sepsis

Sjogren's syndrome
(preparation of Ph benzoyl pyrazoles as CRTH2 receptor ligands)

IT 304450-03-1P 328572-06-1P 330820-00-3P 418800-77-8P 418801-66-8P
700848-40-4P 850811-67-5P 870809-73-7P 870809-74-8P 870809-75-9P
870809-76-0P 870809-77-1P 870809-78-2P 870809-79-3P 870809-80-6P
870809-81-7P 870809-82-8P 870809-83-9P 870809-84-0P 870809-85-1P
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870809-91-9P 870809-92-0P 870809-93-1P 870809-94-2P 870809-95-3P
870809-96-4P 870809-97-5P 870809-98-6P 870809-99-7P 870810-00-7P
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870810-57-4P 870810-58-5P 870810-59-6P 870810-60-9P 870810-61-0P
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870810-77-8P 870810-78-9P 870810-79-0P 870810-80-3P 870810-81-4P
870810-82-5P 870810-83-6P 870810-84-7P 870810-85-8P 870810-86-9P
870810-87-0P 870810-88-1P 870810-89-2P 870810-90-5P 870810-91-6P
870810-92-7P 870810-93-8P 870810-94-9P 870810-95-0P 870810-96-1P
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870811-02-2P 870811-03-3P 870811-04-4P 870811-05-5P 870811-06-6P
870811-07-7P 870811-08-8P 870811-09-9P 870811-10-2P
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870811-17-9P 870811-18-0P 870811-19-1P 870811-20-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of Ph benzoyl pyrazoles as CRTH2 receptor ligands)

IT 55-21-0, Benzamide 70-11-1, 2-Bromoacetophenone 93-17-4 93-58-3
98-80-6, Phenylboronic acid 100-47-0, Benzonitrile, reactions
100-70-9, 2-Pyridinecarbonitrile 103-81-1, 2-Phenylacetamide 104-47-2
104-81-4, 4-Methylbenzyl bromide 105-36-2, Ethyl bromoacetate
140-29-4, Benzeneacetonitrile 140-53-4 305-15-7 332-25-2 365-34-4,
2-Trifluoromethylphenylhydrazine 368-77-4 368-78-5,
3-Trifluoromethylphenylhydrazine 368-90-1 455-18-5 459-22-3
535-11-5, Ethyl 2-bromopropionate 536-38-9 555-96-4 589-21-9,
4-Bromophenylhydrazine 590-17-0, Bromoacetonitrile 603-77-0 610-96-8
611-17-6, 2-Chlorobenzylbromide 615-00-9 619-56-7, 4-Chlorobenzamide
622-95-7, 4-Chlorobenzyl bromide 623-03-0 623-33-6 729-17-9
766-80-3, 3-Chlorobenzyl bromide 766-84-7 873-32-5 874-90-8
932-90-1, Benzaldoxime 935-44-4 1066-54-2, (Trimethylsilyl)acetylene
1126-46-1 1194-02-1 1194-65-6 1450-75-5, 5'-Bromo-2'-
hydroxyacetophenone 1527-89-5 1529-41-5 1679-18-1,
4-Chlorophenylboronic acid 1761-61-1 1943-82-4 2227-79-4,
Benzenecarbothioamide 2243-55-2 **2295-31-0**,
2,4-Thiazolidinedione 2368-80-1, 2-Fluorophenylhydrazine 2856-63-5
2905-65-9 2947-61-7 3038-47-9 3096-81-9 3215-64-3 3218-49-3
3424-93-9, 4-Methoxybenzamide 3471-32-7, 4-Methoxyphenylhydrazine
4068-76-2 4426-47-5, Butylboronic acid 4930-98-7, 2-Hydrazinopyridine
5329-12-4, 2,4,6-Trichlorophenylhydrazine 5813-86-5, 3-Methoxybenzamide

6306-60-1 6343-93-7 6574-98-7, 2,4-Dichlorobenzonitrile 6609-56-9
7035-03-2 10449-07-7, 2-Chlorophenylhydrazine 13123-92-7,
2,4-Dichlorophenylhydrazine 13124-18-0 13388-75-5 13957-54-5
14763-20-3, 3-Chlorophenylhydrazine 14763-24-7, 2,6-
Dichlorophenylhydrazine 16732-66-4, 2-Bromophenylhydrazine 17518-48-8
17672-29-6 18312-46-4 18463-71-3 19275-55-9, 2-Ethylphenylhydrazine
19924-43-7 20443-98-5, 2,6-Dichlorobenzylbromide 25025-06-3
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33695-58-8, 4-Ethylbenzamide 40887-80-7, 3-Bromophenylhydrazine
42059-78-9 42059-80-3 49561-96-8 49619-58-1 52817-12-6,
6-Bromo-3-formylchromone 54751-01-8, 4-Bromomethylpyridine 57279-78-4,
2,4-Dibromophenylhydrazine 58711-28-7 58791-94-9 60283-38-7
61466-44-2 61466-46-4 63589-18-4 67156-57-4 68287-72-9
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870811-33-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of Ph benzoyl pyrazoles as CRTH2 receptor ligands)

IT 34849-50-8P 51336-47-1P 93065-69-1P 93065-72-6P 850811-66-4P
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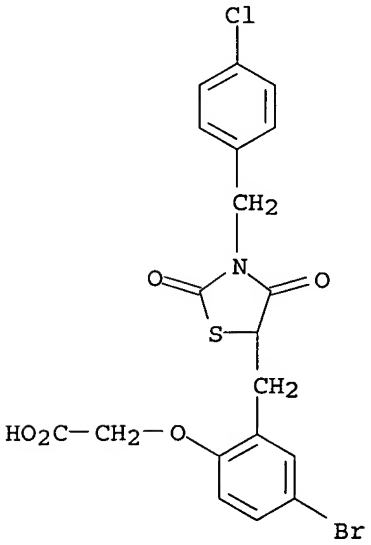
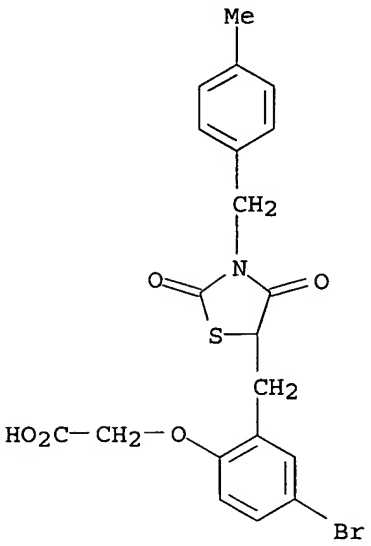
870811-27-1P 870811-28-2P 870811-29-3P **870811-30-6P**
870811-31-7P 870811-34-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of Ph benzoyl pyrazoles as CRTH2 receptor ligands)

IT **870811-11-3P 870811-12-4P 870811-13-5P**
870811-14-6P 870811-15-7P 870811-16-8P
870811-17-9P 870811-18-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of Ph benzoyl pyrazoles as CRTH2 receptor ligands)

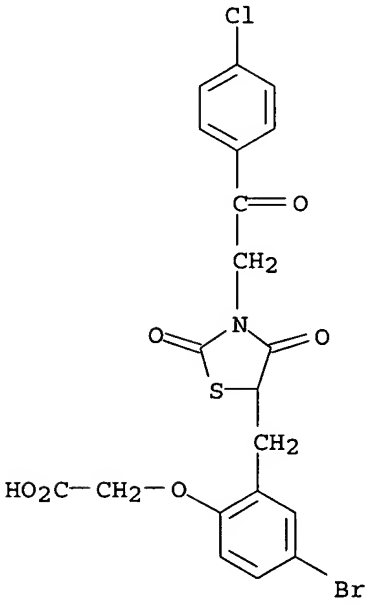
RN 870811-11-3 CAPLUS
CN Acetic acid, [4-bromo-2-[[3-[(4-chlorophenyl)methyl]-2,4-dioxo-5-thiazolidinyl]methyl]phenoxy]- (9CI) (CA INDEX NAME)



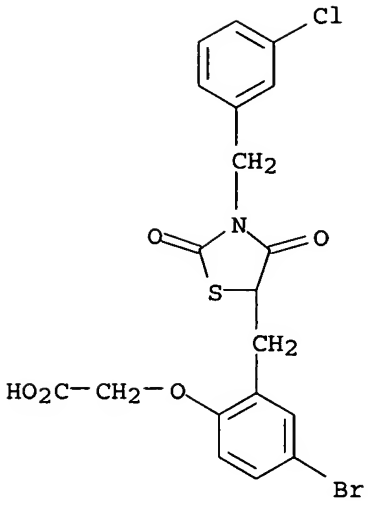
RN 870811-12-4 CAPLUS
CN Acetic acid, [4-bromo-2-[[3-[(4-methylphenyl)methyl]-2,4-dioxo-5-thiazolidinyl]methyl]phenoxy]- (9CI) (CA INDEX NAME)



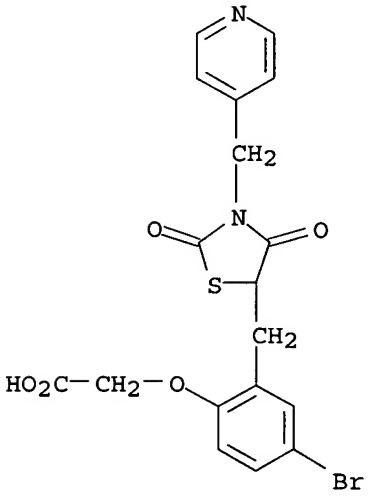
RN 870811-13-5 CAPLUS
CN Acetic acid, [4-bromo-2-[[3-[2-(4-chlorophenyl)-2-oxoethyl]-2,4-dioxo-5-thiazolidinyl]methyl]phenoxy]- (9CI) (CA INDEX NAME)



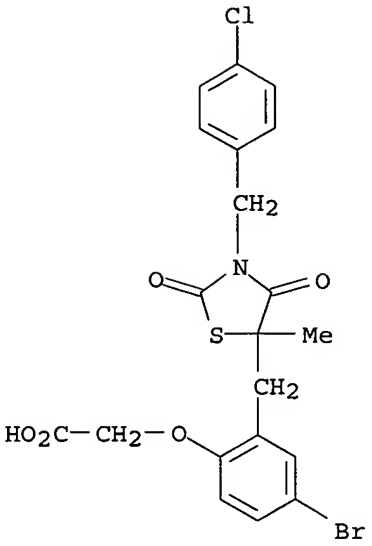
RN 870811-14-6 CAPLUS
CN Acetic acid, [4-bromo-2-[[3-[(3-chlorophenyl)methyl]-2,4-dioxo-5-thiazolidinyl]methyl]phenoxy]- (9CI) (CA INDEX NAME)



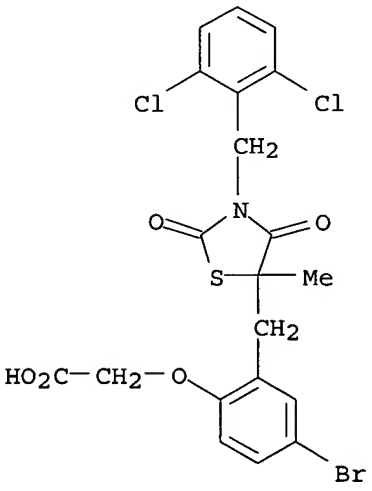
RN 870811-15-7 CAPLUS
CN Acetic acid, [4-bromo-2-[[2,4-dioxo-3-(4-pyridinylmethyl)-5-thiazolidinyl]methyl]phenoxy]- (9CI) (CA INDEX NAME)



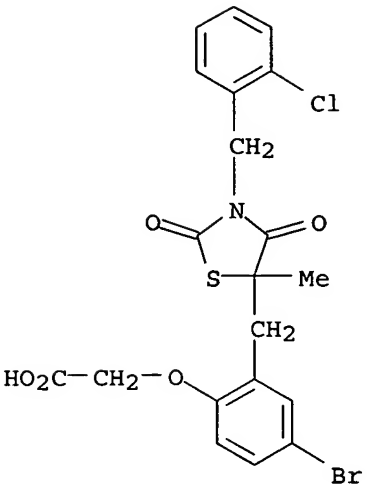
RN 870811-16-8 CAPLUS
CN Acetic acid, [4-bromo-2-[[3-[(4-chlorophenyl)methyl]-5-methyl-2,4-dioxo-5-thiazolidinyl]methyl]phenoxy]- (9CI) (CA INDEX NAME)



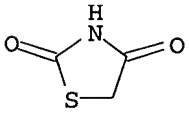
RN 870811-17-9 CAPLUS
CN Acetic acid, [4-bromo-2-[[3-[(2,6-dichlorophenyl)methyl]-5-methyl-2,4-dioxo-5-thiazolidinyl]methyl]phenoxy]- (9CI) (CA INDEX NAME)



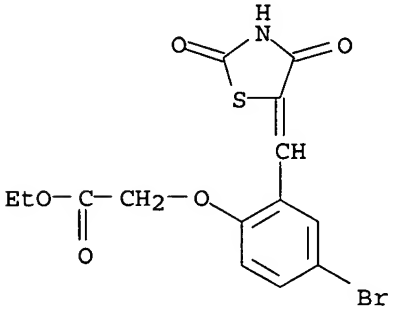
RN 870811-18-0 CAPLUS
CN Acetic acid, [4-bromo-2-[[3-[(2-chlorophenyl)methyl]-5-methyl-2,4-dioxo-5-thiazolidinyl]methyl]phenoxy]- (9CI) (CA INDEX NAME)



IT **2295-31-0**, 2,4-Thiazolidinedione
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of Ph benzoyl pyrazoles as CRTH2 receptor ligands)
RN 2295-31-0 CAPLUS
CN 2,4-Thiazolidinedione (8CI, 9CI) (CA INDEX NAME)



IT **870811-30-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of Ph benzoyl pyrazoles as CRTH2 receptor ligands)
RN 870811-30-6 CAPLUS
CN Acetic acid, [4-bromo-2-[(2,4-dioxo-5-thiazolidinylidene)methyl]phenoxy]-, ethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L148 ANSWER 3 OF 56 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1154777 CAPLUS

DOCUMENT NUMBER: 143:433974
TITLE: Gene expression profiling and markers for use in the assessment of hepatotoxicity
INVENTOR(S): Porter, Mark; Higgs, Brandon; Mendrick, Donna; Elashoff, Michael
PATENT ASSIGNEE(S): Gene Logic, Inc., USA
SOURCE: PCT Int. Appl., 264 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005100989	A2	20051027	WO 2005-US11532	20050407

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-559949P P 20040407

AB Methods of using the effects of a substance on gene expression profiles are described for use in assessing their toxicity, especially hepatotoxicity, are described. The invention also includes microarrays, computer systems comprising the toxicity prediction models, as well as methods of using the computer systems by remote users for determining the toxicity of test agents.

A database of gene expression profiles for rat liver using a broad range of drugs, com. chems., and known poisons is developed.

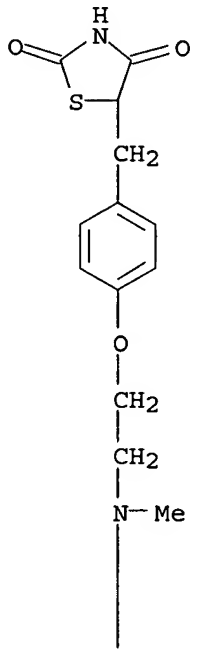
IC ICM G01N033-52
CC 4-1 (Toxicology)
Section cross-reference(s): 3
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(FXYD domain-containing **ion transport** regulator 1, gene for, expression of, as marker in toxicol. testing; gene expression profiling and markers for use in assessment of hepatotoxicity)
IT 50-06-6, Phenobarbital 50-48-6 50-78-2 51-61-6, Dopamine 53-86-1, Indomethacin 53-96-3 54-85-3 55-18-5 56-23-5 56-49-5 57-47-6, Physostigmine 57-63-6 57-92-1 58-27-5 58-73-1 59-05-2 60-54-8 62-44-2 62-55-5, Ethanethioamide 62-75-9 64-17-5, Ethanol 64-86-8 67-66-3 69-65-8, D-Mannitol 85-00-7 86-84-0 91-80-5 99-66-1 103-90-2 107-18-6, 2-Propen-1-ol, biological studies 108-86-1 113-92-8 127-07-1, Hydroxyurea 127-33-3 298-46-4, 5H-Dibenz[b,f]azepine-5-carboxamide 315-22-0 321-64-2, Tacrine 427-51-0 555-30-6 637-07-0 657-24-9 1403-66-3, Gentamicin 1746-01-6, TCDD 1951-25-3 3056-17-5 3521-62-8 4685-14-7 6621-47-2 7261-97-4 7440-69-9D, Bismuth, compds. 10540-29-1 11097-69-1, PCB 1254 13073-35-3 13292-46-1, Rifampin 13311-84-7, Flutamide 15307-86-5 18378-89-7, Plicamycin 22494-42-4 25451-15-4 25812-30-0, Gemfibrozil 30516-87-1 33419-42-0 34911-55-2 36894-69-6 38194-50-2 49562-28-9 49780-10-1, AY 25329 50892-23-4

52214-84-3 56420-45-2 57574-09-1 72558-82-8, Ceftazidime
72559-06-9, Rifabutin 75330-75-5 76824-35-6 79902-63-9, Simvastatin
85622-93-1, Temozolomide 90357-06-5, Bicalutamide 111406-87-2,
Zileuton 120011-70-3 **122320-73-4**, Rosiglitazone 132138-76-2
136470-78-5 868588-24-3, CZB 777
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(assessing hepatotoxicity of; gene expression profiling and markers for use in assessment of hepatotoxicity)

IT **122320-73-4**, Rosiglitazone
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(assessing hepatotoxicity of; gene expression profiling and markers for use in assessment of hepatotoxicity)

RN 122320-73-4 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



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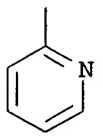
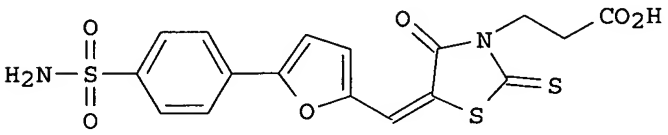


L148 ANSWER 4 OF 56 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:902661 CAPLUS

DOCUMENT NUMBER: 143:242025
TITLE: Methods using heterocyclic compounds for modulating neurotrophin-mediated activity
INVENTOR(S): Ross, Gregory M.; Szarek, Walter A.; Vohra, Rahul
PATENT ASSIGNEE(S): Painceptor Pharma Corporation, Can.; Queen's University At Kingston
SOURCE: PCT Int. Appl., 152 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005076695	A2	20050825	WO 2005-IB1050	20050211
WO 2005076695	A3	20051013		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005282840	A1	20051222	US 2005-57084	20050211
PRIORITY APPLN. INFO.:			US 2004-544267P P	20040211
			US 2004-564106P P	20040420

OTHER SOURCE(S): MARPAT 143:242025
GI



I

AB Heterocyclic compds. and compns. are disclosed which modulate the interaction of nerve growth factor and brain-derived neurotrophic factor with neurotrophic receptors. Also disclosed are methods of using the compns. of the invention, including methods of administration. Reaction schemes for selected compds., e.g. I, are included.

IC ICM A61K
CC 1-11 (Pharmacology)
Section cross-reference(s): 28
IT Alzheimer's disease
Analgesics
Anesthetics
Anti-Alzheimer's agents
Anti-infective agents
Anti-inflammatory agents
Antiarrhythmics
Antiarthritics
Antiasthmatics

Antibacterial agents
Anticonvulsants
Antidepressants
Antiemetics
Antiglaucoma agents
Antiparkinsonian agents
Antipsychotics
Antitumor agents
Antiulcer agents
Antiviral agents
Cardiovascular agents
Combination chemotherapy
Connective tissue, disease
Cystic fibrosis
Dermatitis
Drug dependence
Epilepsy
Gastrointestinal agents
Glaucoma (disease)
Headache
Inflammation
Multiple sclerosis
Musculoskeletal diseases
Myositis
Nausea
Nervous system, disease
Nervous system agents
Pain
Parkinson's disease
Psychotropics
Respiratory distress syndrome
Schizophrenia
Urogenital system, disease
(heterocyclic compds. for modulating neurotrophin-mediated activity)

IT **306279-33-4P** 423145-71-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(heterocyclic compds. for modulating neurotrophin-mediated activity)

IT 153854-74-1 **247068-04-8** 260780-42-5 **292172-67-9**
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425625-57-6 425656-08-2 428447-04-5 **428858-13-3**
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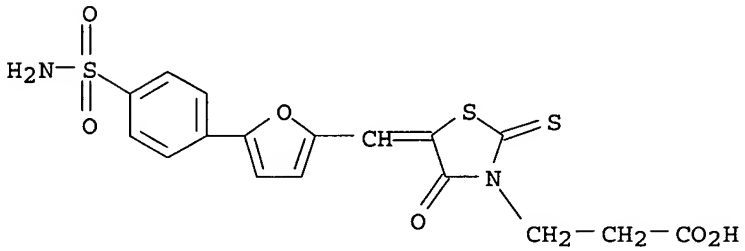
431932-24-0 **431941-25-2** **431977-82-1**
431978-00-6 **431978-60-8** 431979-54-3

432002-09-0 **432018-88-7** **432502-90-4**
432509-78-9 **432514-76-6** **433237-80-0**
433239-57-7 **433240-28-9** 443323-11-3 444668-10-4
444782-83-6 471264-16-1 **500134-94-1** 528831-33-6
529481-81-0 **573938-94-0** 577694-47-4 577962-14-2
578697-94-6 **591224-15-6** **591224-26-9** 591726-08-8
591726-12-4 591726-13-5 591726-24-8 592512-17-9 593265-17-9
593266-13-8 **593272-19-6** 593274-57-8 593274-59-0
593275-67-3 643746-15-0 664351-95-5 664357-58-8
666714-18-7 666714-19-8 666714-20-1 675166-72-0 **676643-59-7**
677309-99-8 678167-51-6 679413-88-8 685132-05-2 690670-27-0
690670-87-2 690672-35-6 690677-63-5 **690686-89-6**
690686-93-2 690697-31-5 **690702-76-2** 690987-80-5
692266-45-8 692267-66-6 692269-83-3 **692270-02-3**
692277-30-8 692277-39-7 692282-53-4 758687-37-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(heterocyclic compds. for modulating neurotrophin-mediated activity)

IT **141-84-4** 21821-40-9 60875-16-3 415943-88-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(heterocyclic compds. for modulating neurotrophin-mediated activity)

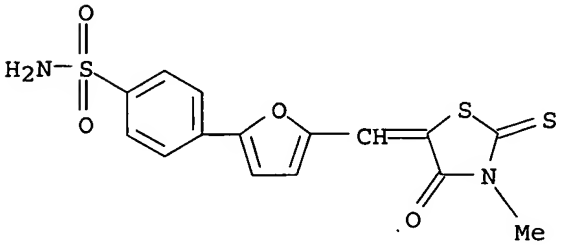
IT **306279-33-4P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(heterocyclic compds. for modulating neurotrophin-mediated activity)

RN 306279-33-4 CAPLUS
CN 3-Thiazolidinepropanoic acid, 5-[[5-[4-(aminosulfonyl)phenyl]-2-furanyl]methylene]-4-oxo-2-thioxo- (9CI) (CA INDEX NAME)

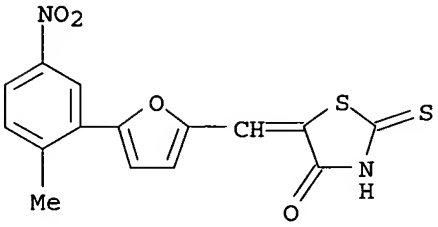


IT **247068-04-8** **292172-67-9** **292640-65-4**
292640-66-5 **299905-23-0** **300377-05-3**
301681-81-2 **306318-97-8** **307324-90-9**
307552-75-6 **312716-52-2** **324565-42-6**
324566-90-7 **327032-88-2** **327033-04-5**
329001-82-3 **329001-85-6** **329002-11-1**
331640-04-1 **331652-49-4** **339015-48-4**
344944-94-1 **366459-92-9** **373611-94-0**
387359-41-3 **387873-49-6** **388079-86-5**
425615-56-1 **428858-13-3** **431928-32-4**
431932-02-4 **431941-25-2** **431977-82-1**
431978-00-6 **431978-60-8** **432002-09-0**
432018-88-7 **432502-90-4** **432509-78-9**
432514-76-6 **433237-80-0** **433240-28-9**
500134-94-1 **573938-94-0** **591224-15-6**
591224-26-9 **593266-13-8** **593272-19-6**
593275-67-3 **676643-59-7** **690686-89-6**
690686-93-2 **690702-76-2** **692266-45-8**

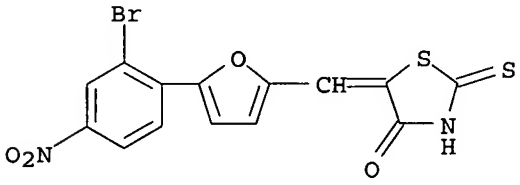
692270-02-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(heterocyclic compds. for modulating neurotrophin-mediated activity)
RN 247068-04-8 CAPLUS
CN Benzenesulfonamide, 4-[5-[(3-methyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl]-2-furanyl]- (9CI) (CA INDEX NAME)



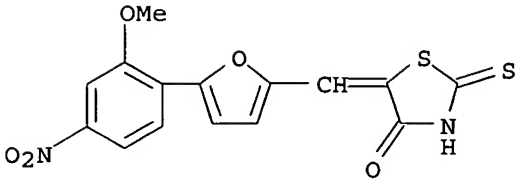
RN 292172-67-9 CAPLUS
CN 4-Thiazolidinone, 5-[[5-(2-methyl-5-nitrophenyl)-2-furanyl]methylene]-2-thioxo- (9CI) (CA INDEX NAME)



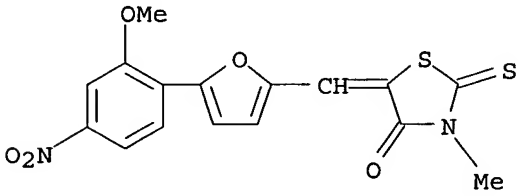
RN 292640-65-4 CAPLUS
CN 4-Thiazolidinone, 5-[[5-(2-bromo-4-nitrophenyl)-2-furanyl]methylene]-2-thioxo- (9CI) (CA INDEX NAME)



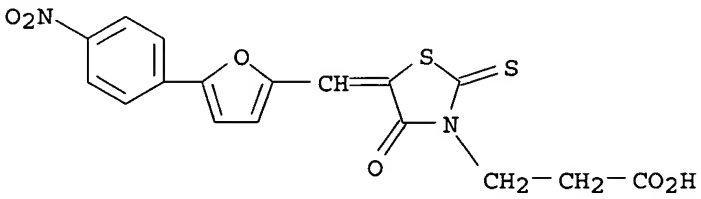
RN 292640-66-5 CAPLUS
CN 4-Thiazolidinone, 5-[[5-(2-methoxy-4-nitrophenyl)-2-furanyl]methylene]-2-thioxo- (9CI) (CA INDEX NAME)



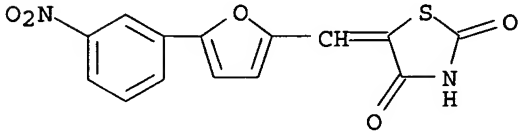
RN 299905-23-0 CAPLUS
CN 4-Thiazolidinone, 5-[[5-(2-methoxy-4-nitrophenyl)-2-furanyl]methylene]-3-methyl-2-thioxo- (9CI) (CA INDEX NAME)



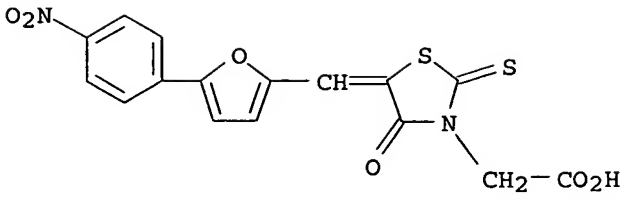
RN 300377-05-3 CAPLUS
CN 3-Thiazolidinepropanoic acid, 5-[[5-(4-nitrophenyl)-2-furanyl]methylene]-4-oxo-2-thioxo- (9CI) (CA INDEX NAME)



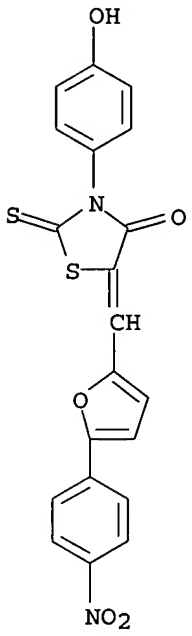
RN 301681-81-2 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[5-(3-nitrophenyl)-2-furanyl]methylene]- (9CI) (CA INDEX NAME)



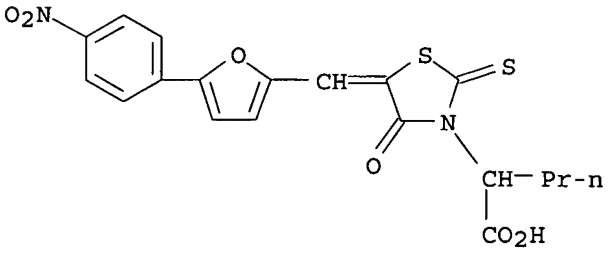
RN 306318-97-8 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(4-nitrophenyl)-2-furanyl]methylene]-4-oxo-2-thioxo- (9CI) (CA INDEX NAME)



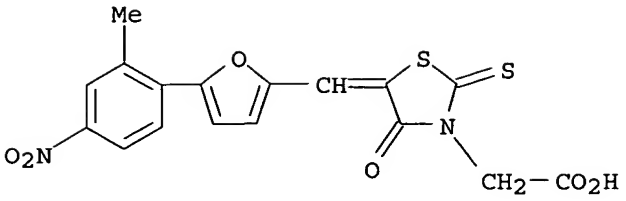
RN 307324-90-9 CAPLUS
CN 4-Thiazolidinone, 3-(4-hydroxyphenyl)-5-[[5-(4-nitrophenyl)-2-furanyl]methylene]-2-thioxo- (9CI) (CA INDEX NAME)



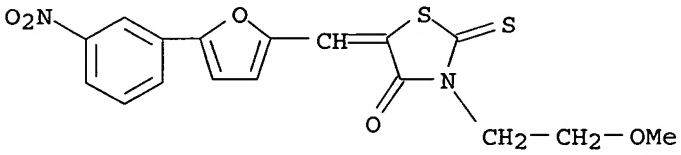
RN 307552-75-6 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(4-nitrophenyl)-2-furanyl]methylene]-4-oxo-α-propyl-2-thioxo- (9CI) (CA INDEX NAME)



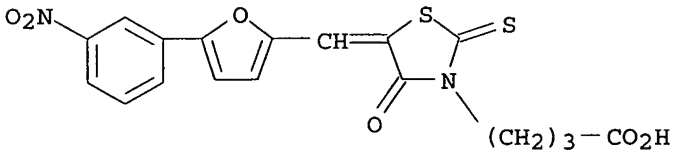
RN 312716-52-2 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(2-methyl-4-nitrophenyl)-2-furanyl]methylene]-4-oxo-2-thioxo- (9CI) (CA INDEX NAME)



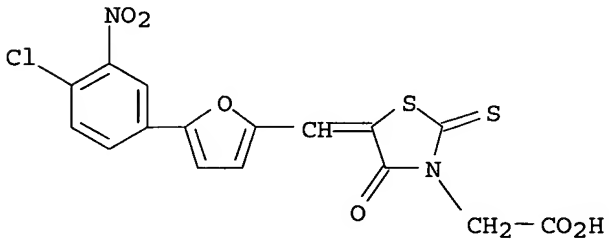
RN 324565-42-6 CAPLUS
CN 4-Thiazolidinone, 3-(2-methoxyethyl)-5-[[5-(3-nitrophenyl)-2-furanyl]methylene]-2-thioxo- (9CI) (CA INDEX NAME)



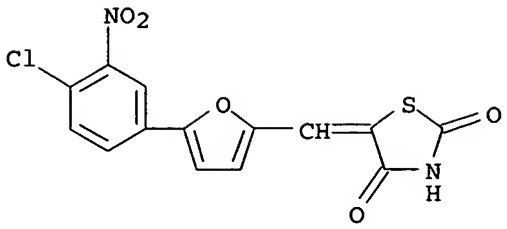
RN 324566-90-7 CAPLUS
CN 3-Thiazolidinebutanoic acid, 5-[[5-(3-nitrophenyl)-2-furanyl]methylene]-4-oxo-2-thioxo- (9CI) (CA INDEX NAME)



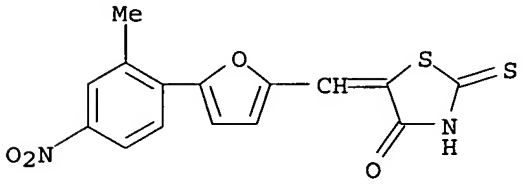
RN 327032-88-2 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(4-chloro-3-nitrophenyl)-2-furanyl]methylene]-4-oxo-2-thioxo- (9CI) (CA INDEX NAME)



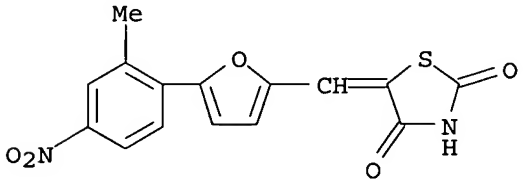
RN 327033-04-5 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[5-(4-chloro-3-nitrophenyl)-2-furanyl]methylene]- (9CI) (CA INDEX NAME)



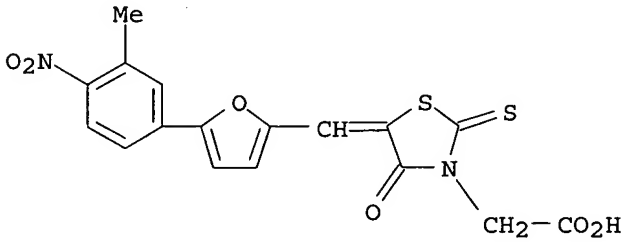
RN 329001-82-3 CAPLUS
CN 4-Thiazolidinone, 5-[[5-(2-methyl-4-nitrophenyl)-2-furanyl]methylene]-2-thioxo- (9CI) (CA INDEX NAME)



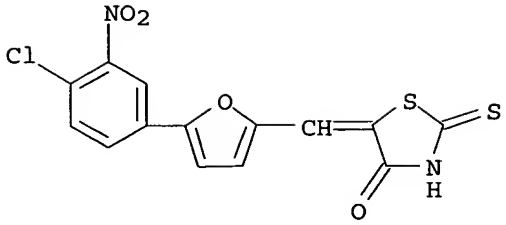
RN 329001-85-6 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[5-(2-methyl-4-nitrophenyl)-2-furanyl]methylene]- (9CI) (CA INDEX NAME)



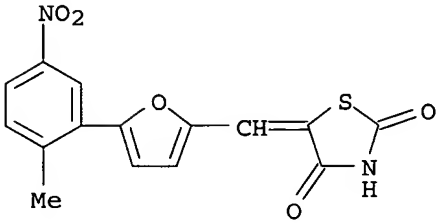
RN 329002-11-1 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(3-methyl-4-nitrophenyl)-2-furanyl]methylene]-4-oxo-2-thioxo- (9CI) (CA INDEX NAME)



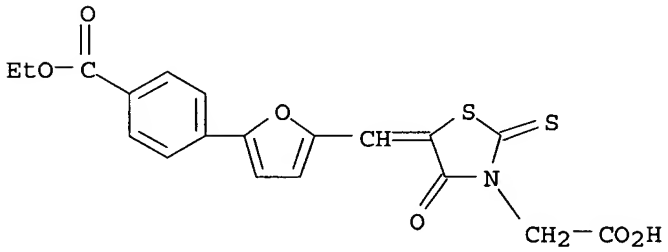
RN 331640-04-1 CAPLUS
CN 4-Thiazolidinone, 5-[[5-(4-chloro-3-nitrophenyl)-2-furanyl]methylene]-2-thioxo- (9CI) (CA INDEX NAME)



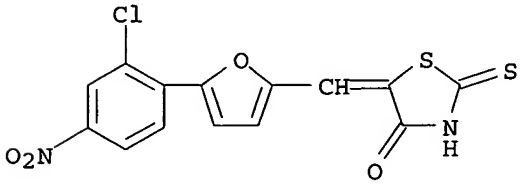
RN 331652-49-4 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[5-(2-methyl-5-nitrophenyl)-2-furanyl]methylene]- (9CI) (CA INDEX NAME)



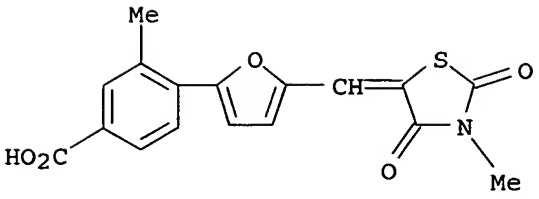
RN 339015-48-4 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-[4-(ethoxycarbonyl)phenyl]-2-furanyl]methylene]-4-oxo-2-thioxo- (9CI) (CA INDEX NAME)



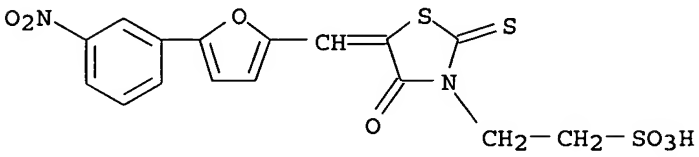
RN 344944-94-1 CAPLUS
CN 4-Thiazolidinone, 5-[[5-(2-chloro-4-nitrophenyl)-2-furanyl]methylene]-2-thioxo- (9CI) (CA INDEX NAME)



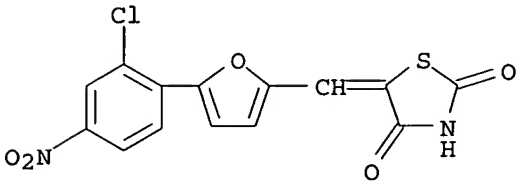
RN 366459-92-9 CAPLUS
CN Benzoic acid, 3-methyl-4-[5-[(3-methyl-2,4-dioxo-5-thiazolidinylidene)methyl]-2-furanyl]- (9CI) (CA INDEX NAME)



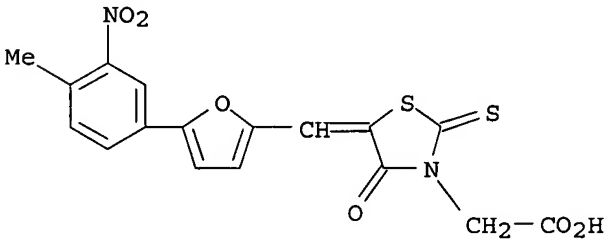
RN 373611-94-0 CAPLUS
CN 3-Thiazolidineethanesulfonic acid, 5-[[5-(3-nitrophenyl)-2-furanyl]methylene]-4-oxo-2-thioxo- (9CI) (CA INDEX NAME)



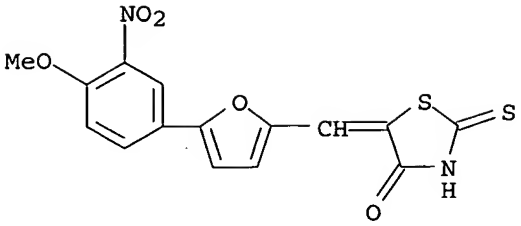
RN 387359-41-3 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[5-(2-chloro-4-nitrophenyl)-2-furanyl]methylene]- (9CI) (CA INDEX NAME)



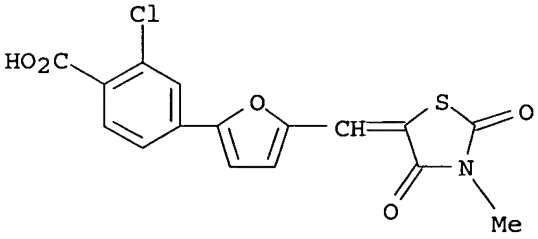
RN 387873-49-6 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(4-methyl-3-nitrophenyl)-2-furanyl]methylene]-4-oxo-2-thioxo- (9CI) (CA INDEX NAME)



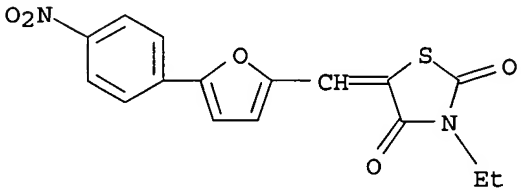
RN 388079-86-5 CAPLUS
CN 4-Thiazolidinone, 5-[[5-(4-methoxy-3-nitrophenyl)-2-furanyl]methylene]-2-thioxo- (9CI) (CA INDEX NAME)



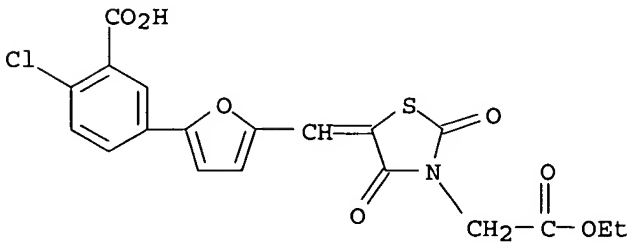
RN 425615-56-1 CAPLUS
CN Benzoic acid, 2-chloro-4-[5-[(3-methyl-2,4-dioxo-5-thiazolidinylidene)methyl]-2-furanyl]- (9CI) (CA INDEX NAME)



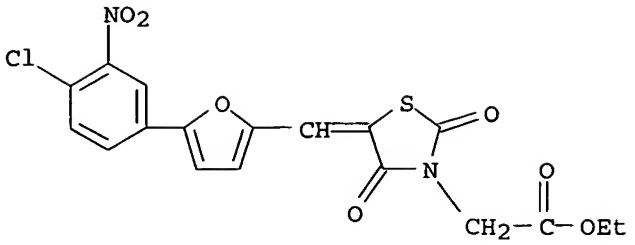
RN 428858-13-3 CAPLUS
CN 2,4-Thiazolidinedione, 3-ethyl-5-[[5-(4-nitrophenyl)-2-furanyl]methylene]- (9CI) (CA INDEX NAME)



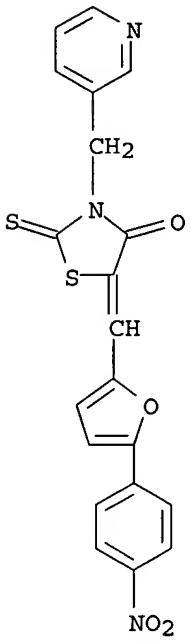
RN 431928-32-4 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(3-carboxy-4-chlorophenyl)-2-furanyl]methylene]-2,4-dioxo-, α-ethyl ester (9CI) (CA INDEX NAME)



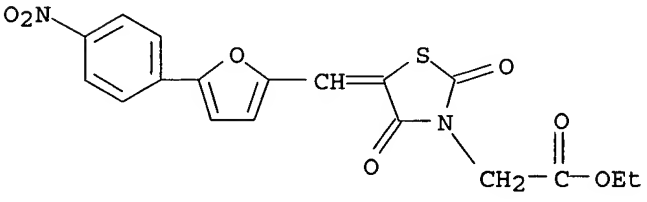
RN 431932-02-4 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(4-chloro-3-nitrophenyl)-2-furanyl]methylene]-2,4-dioxo-, ethyl ester (9CI) (CA INDEX NAME)



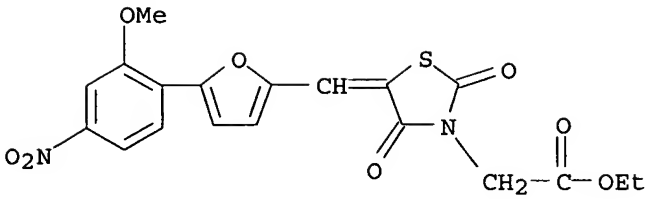
RN 431941-25-2 CAPLUS
CN 4-Thiazolidinone, 5-[[5-(4-nitrophenyl)-2-furanyl]methylene]-3-(3-pyridinylmethyl)-2-thioxo- (9CI) (CA INDEX NAME)



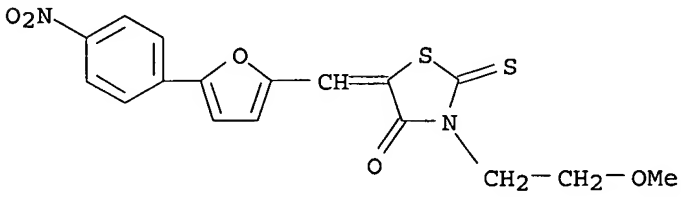
RN 431977-82-1 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(4-nitrophenyl)-2-furanyl]methylene]-2,4-dioxo-, ethyl ester (9CI) (CA INDEX NAME)



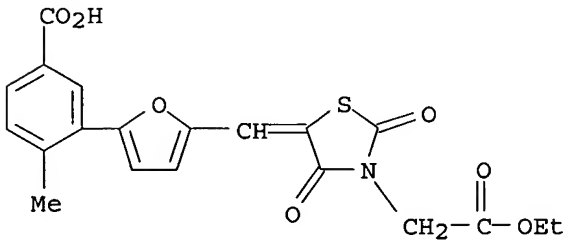
RN 431978-00-6 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(2-methoxy-4-nitrophenyl)-2-furanyl]methylene]-2,4-dioxo-, ethyl ester (9CI) (CA INDEX NAME)



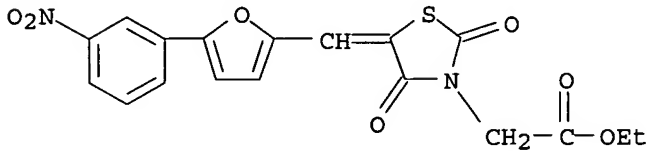
RN 431978-60-8 CAPLUS
CN 4-Thiazolidinone, 3-(2-methoxyethyl)-5-[[5-(4-nitrophenyl)-2-furanyl]methylene]-2-thioxo- (9CI) (CA INDEX NAME)



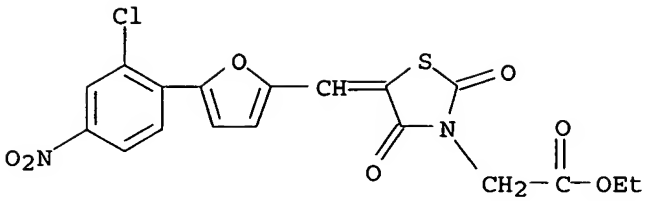
RN 432002-09-0 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(5-carboxy-2-methylphenyl)-2-furanyl]methylene]-2,4-dioxo-, α-ethyl ester (9CI) (CA INDEX NAME)



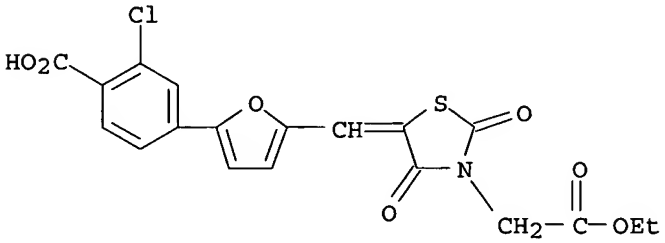
RN 432018-88-7 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(3-nitrophenyl)-2-furanyl]methylene]-2,4-dioxo-, ethyl ester (9CI) (CA INDEX NAME)



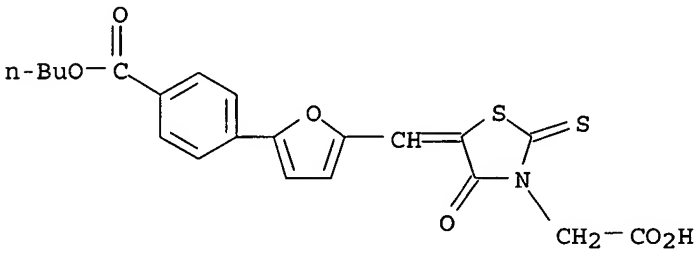
RN 432502-90-4 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(2-chloro-4-nitrophenyl)-2-furanyl]methylene]-2,4-dioxo-, ethyl ester (9CI) (CA INDEX NAME)



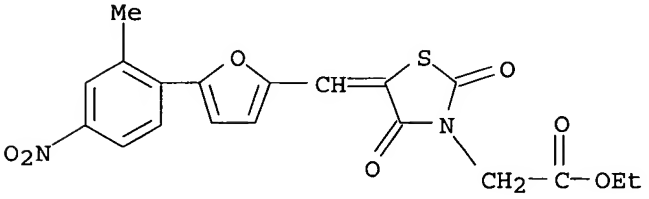
RN 432509-78-9 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(4-carboxy-3-chlorophenyl)-2-furanyl]methylene]-2,4-dioxo-, α-ethyl ester (9CI) (CA INDEX NAME)



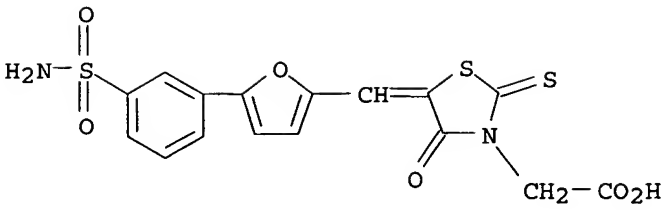
RN 432514-76-6 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-[4-(butoxycarbonyl)phenyl]-2-furanyl]methylene]-4-oxo-2-thioxo- (9CI) (CA INDEX NAME)



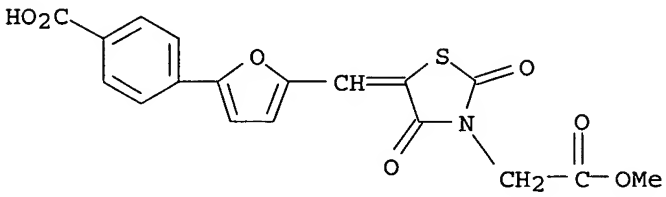
RN 433237-80-0 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(2-methyl-4-nitrophenyl)-2-furanyl]methylene]-2,4-dioxo-, ethyl ester (9CI) (CA INDEX NAME)



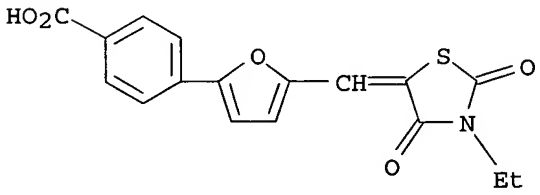
RN 433240-28-9 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-[3-(aminosulfonyl)phenyl]-2-furanyl]methylene]-4-oxo-2-thioxo- (9CI) (CA INDEX NAME)



RN 500134-94-1 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(4-carboxyphenyl)-2-furanyl]methylene]-2,4-dioxo-, α-methyl ester (9CI) (CA INDEX NAME)

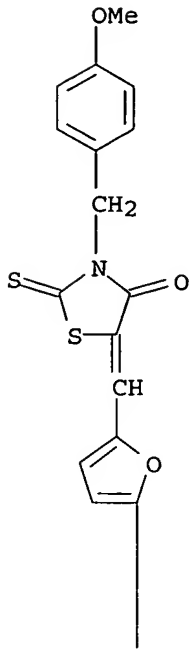


RN 573938-94-0 CAPLUS
CN Benzoic acid, 4-[5-[(3-ethyl-2,4-dioxo-5-thiazolidinylidene)methyl]-2-furanyl]- (9CI) (CA INDEX NAME)

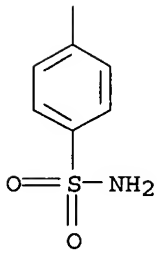


RN 591224-15-6 CAPLUS
CN Benzenesulfonamide, 4-[5-[[3-[(4-methoxyphenyl)methyl]-4-oxo-2-thioxo-5-thiazolidinylidene]methyl]-2-furanyl]- (9CI) (CA INDEX NAME)

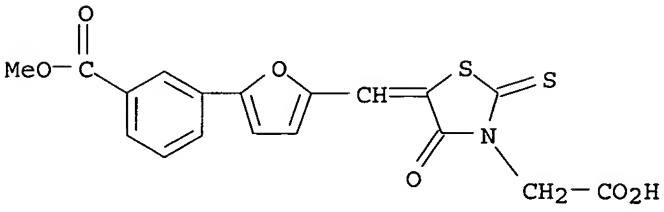
PAGE 1-A



PAGE 2-A

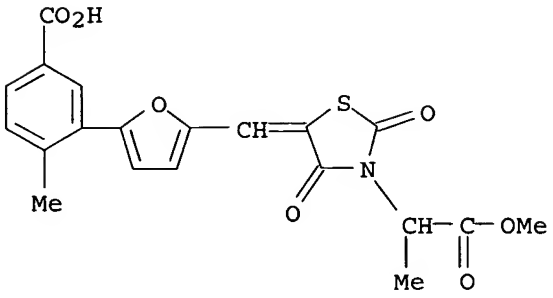


RN 591224-26-9 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-[3-(methoxycarbonyl)phenyl]-2-furanyl]methylene]-4-oxo-2-thioxo- (9CI) (CA INDEX NAME)

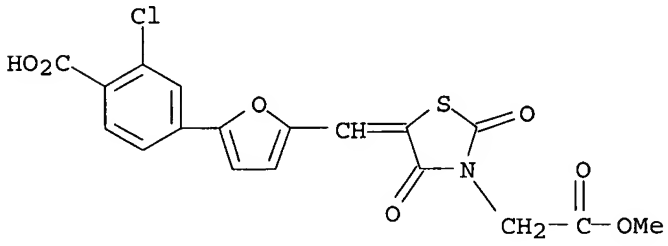


RN 593266-13-8 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(5-carboxy-2-methylphenyl)-2-

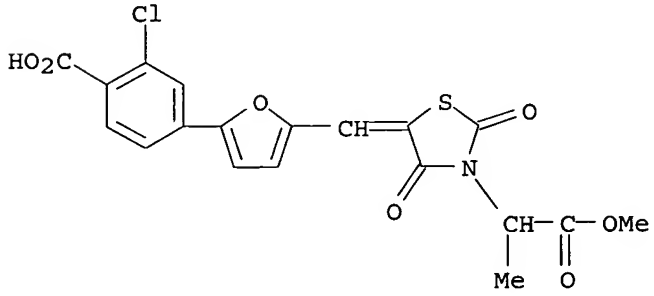
furanyl]methylene]-α-methyl-2,4-dioxo-, α-methyl ester (9CI)
(CA INDEX NAME)



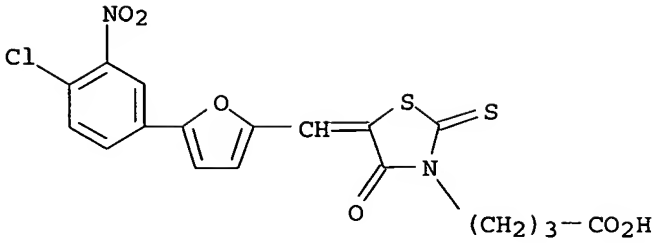
RN 593272-19-6 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(4-carboxy-3-chlorophenyl)-2-furanyl]methylene]-2,4-dioxo-, α-methyl ester (9CI) (CA INDEX NAME)



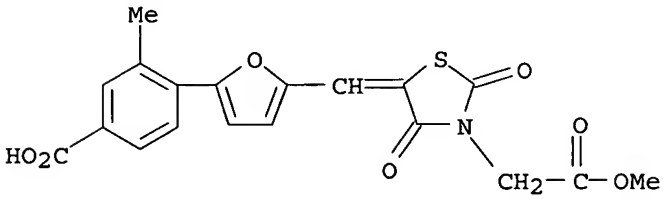
RN 593275-67-3 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(4-carboxy-3-chlorophenyl)-2-furanyl]methylene]-α-methyl-2,4-dioxo-, α-methyl ester (9CI)
(CA INDEX NAME)



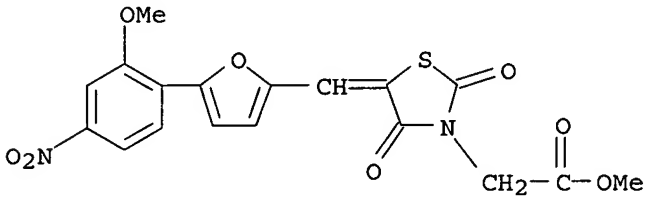
RN 676643-59-7 CAPLUS
CN 3-Thiazolidinebutanoic acid, 5-[[5-(4-chloro-3-nitrophenyl)-2-furanyl]methylene]-4-oxo-2-thioxo- (9CI) (CA INDEX NAME)



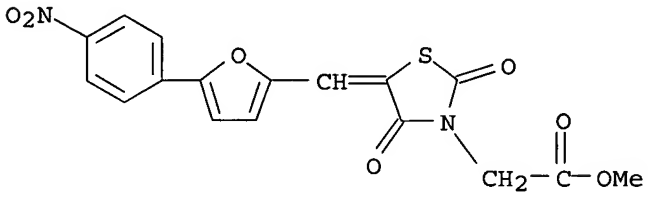
RN 690686-89-6 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(4-carboxy-2-methylphenyl)-2-furanyl]methylene]-2,4-dioxo-, α-methyl ester (9CI) (CA INDEX NAME)



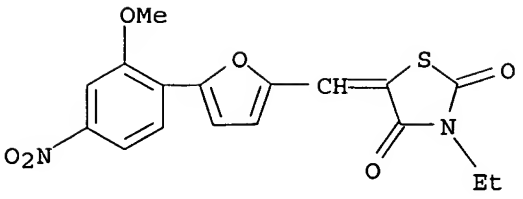
RN 690686-93-2 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(2-methoxy-4-nitrophenyl)-2-furanyl]methylene]-2,4-dioxo-, methyl ester (9CI) (CA INDEX NAME)



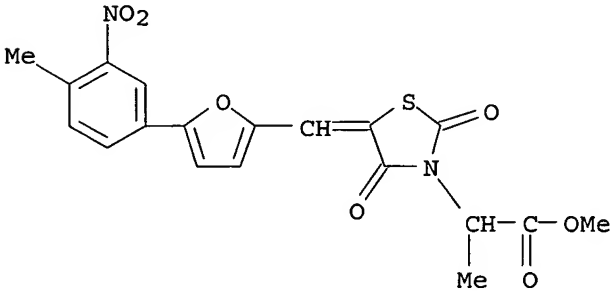
RN 690702-76-2 CAPLUS
CN 3-Thiazolidineacetic acid, 5-[[5-(4-nitrophenyl)-2-furanyl]methylene]-2,4-dioxo-, methyl ester (9CI) (CA INDEX NAME)



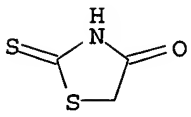
RN 692266-45-8 CAPLUS
CN 2,4-Thiazolidinedione, 3-ethyl-5-[[5-(2-methoxy-4-nitrophenyl)-2-furanyl]methylene]- (9CI) (CA INDEX NAME)



RN 692270-02-3 CAPLUS
CN 3-Thiazolidineacetic acid, α-methyl-5-[[5-(4-methyl-3-nitrophenyl)-2-furanyl]methylene]-2,4-dioxo-, methyl ester (9CI) (CA INDEX NAME)



IT **141-84-4**
RL: RCT (Reactant); RACT (Reactant or reagent)
(heterocyclic compds. for modulating neurotrophin-mediated activity)
RN 141-84-4 CAPLUS
CN 4-Thiazolidinone, 2-thioxo- (9CI) (CA INDEX NAME)



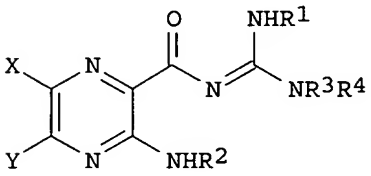
L148 ANSWER 5 OF 56 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:177896 CAPLUS
DOCUMENT NUMBER: 142:280225
TITLE: Preparation of capped aminopyrazinoylguanidines as sodium channel blockers
INVENTOR(S): Johnson, Michael R.; Molino, Bruce F.; Zhang, Jianzhong; Sargent, Bruce J.
PATENT ASSIGNEE(S): Parion Sciences, Inc., USA
SOURCE: PCT Int. Appl., 100 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005018644	A1	20050303	WO 2004-US26885	20040818

WO 2005018644 B1 20050512
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2005080091 A1 20050414 US 2004-920410 20040818
US 2005234072 A1 20051020 US 2005-131262 20050518
US 2005228182 A1 20051013 US 2005-138280 20050527
PRIORITY APPLN. INFO.: US 2003-495725P P 20030818
US 2004-920410 A1 20040818

OTHER SOURCE(S): MARPAT 142:280225
GI



I

AB Title compds. [I; X = H, halo, CF3, alkyl, (substituted) Ph, etc.; Y = H, OH, SH, alkoxy, alkylthio, halo, alkyl, (substituted) aryl, etc.; R1 = H, alkyl; R2 = R7, (CH2)mOR8, (CH2)mNR7R10, (CH2CH2O)mR8, etc.; m = 1-7; R3, R4 = H, alkyl, hydroxyalkyl, Ph, phenylalkyl, naphthylalkyl, pyridylalkyl, etc.; R7 = H, alkyl, (substituted) Ph, etc.; R8 = H, alkyl, 2-tetrahydropyranyl, glucuronide, etc.; R10 = H, SO2Me, COR13, CO2R13, etc.; R13 = H, R7, R10, etc.; with provisos], were prepared Thus, [4-(4-hydroxyphenyl)butyl]carbamic acid benzyl ester in EtOH at 70° was treated with oxiranylmethanol over 4 h to give 4.6% [4-[4-[3-(2,3-dihydroxypropoxy)-2-hydroxypropoxy]phenyl]butyl]carbamic acid benzyl ester. This was hydrogenolyzed in EtOH over Pd/C to give 51% 3-[3-[4-(4-aminobutyl)phenoxy]-2-hydroxypropoxy]propane-1,2-diol. The latter was stirred with Et3N and 1-(3,5-diamino-6-chloropyrazine-2-carbonyl)-2-methylisothiourea hydroiodide in EtOH at 65° to give 36% N-(3,5-diamino-6-chloropyrazine-2-carbonyl)-N'-[4-[4-[3-(2,3-dihydroxypropoxy)-2-hydroxypropoxy]phenyl]butyl]guanidine (PSA 15143). The latter showed Na channel blocking activity with EC50 = 7 nM.

IC ICM A61K031-4965
ICS C07C241-02

CC 28-17 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

ST aminopyrazinoylguanidine capped prepn sodium channel blocker; pyrazinoylguanidine amino chloro prepn dry mucous membrane skin treatment; bronchitis **cystic fibrosis** sinusitis hypertension constipation treatment aminopyrazinoyl guanidine

IT Asthma
Cystic fibrosis
Edema
Emphysema
Hypertension

Sjogren's syndrome
(treatment; preparation of aminopyrazinoylguanidines as sodium channel blockers)

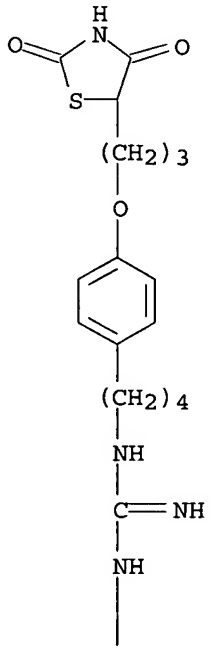
IT **847200-78-6P** 847200-80-0P 847200-82-2P 847200-84-4P
847200-85-5P 847200-86-6P 847200-87-7P 847200-88-8P 847200-89-9P
847200-90-2P 847200-91-3P 847200-92-4P 847200-93-5P 847200-94-6P
847236-78-6P, PSA 17482 847236-85-5P, PSA 16437 847236-86-6P, PSA 16208 847236-87-7P, PSA 15143
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compound; preparation of aminopyrazinoylguanidines as sodium channel blockers)

IT **847200-78-6P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compound; preparation of aminopyrazinoylguanidines as sodium channel blockers)

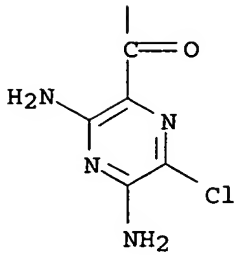
RN 847200-78-6 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[3-(2,4-dioxo-5-thiazolidinyl)propoxy]phenyl]butyl]amino]iminomethyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

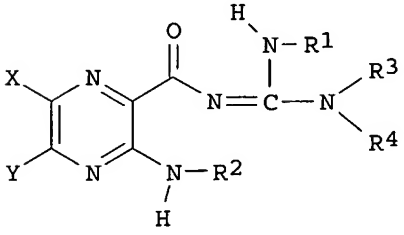


REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L148 ANSWER 6 OF 56 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:158635 CAPLUS
DOCUMENT NUMBER: 142:261557
TITLE: Preparation of cyclic pyrazinoylguanidine sodium channel blockers
INVENTOR(S): Johnson, Michael R.
PATENT ASSIGNEE(S): Parion Sciences, Inc., USA
SOURCE: PCT Int. Appl., 101 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005016879	A2	20050224	WO 2004-US26880	20040818
WO 2005016879	A3	20050602		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005059676	A1	20050317	US 2004-920353	20040818

PRIORITY APPLN. INFO.: US 2003-495720P P 20030818
OTHER SOURCE(S): MARPAT 142:261557
GI



I

AB The title compds. I [X = halo, etc.; Y = H, hydroxyl, etc.; R1 = H, alkyl; R2 = R7, etc.; R3, R4 = H, alkyl, etc.; R7 = (un)substituted Ph, etc], useful as sodium channel blockers (no data), are prepared Thus, N-(3,5-diamino-6-chloropyrazine-2-carbonyl)-N'-[4-[1-(2-hydroxyethyl)piperidin-4-yl]butyl]guanidine dihydrochloride was prepared in a multistep process starting from 4-(piperidin-4-yl)butyric acid HCl salt.

IC ICM C07D

CC 28-17 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

IT Antiasthmatics
Antihypertensives
Asthma
Cystic fibrosis
Diuresis
Diuretics
Edema
Emphysema
Hypertension
Pneumonia
Sjogren's syndrome
Sodium channel blockers
(preparation and use of cyclic pyrazinoylguanidine sodium channel blockers)

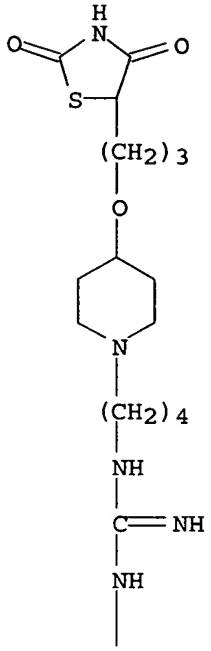
IT 845753-54-0P 845753-55-1P 845753-56-2P 845753-57-3P 845753-58-4P
845753-59-5P 845753-60-8P 845753-61-9P 845753-62-0P 845753-63-1P
845753-64-2P 845753-65-3P 845753-66-4P 845753-67-5P 845753-68-6P
845753-69-7P 845753-70-0P 845753-71-1P 845753-72-2P 845753-73-3P
845753-74-4P 845753-75-5P 845753-76-6P 845753-77-7P
845753-78-8P 845753-79-9P 845753-80-2P 845753-81-3P 845753-82-4P
845753-83-5P 845753-84-6P 845753-85-7P 845753-86-8P 845753-87-9P
845753-88-0P 845753-89-1P, PSA 25452 845753-90-4P, PSA 25569
845753-91-5P 845753-92-6P 845753-93-7P 845753-94-8P 845754-44-1P
845821-02-5P 845821-03-6P 845821-04-7P 845890-72-4P, PSA 25193
845890-73-5P, PSA 25310 845890-75-7P, PSA 25455 845890-76-8P, PSA 25510 845890-89-3P, PSA 25456 845890-90-6P, PSA 25795
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of cyclic pyrazinoylguanidine sodium channel blockers)

IT **845753-74-4P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of cyclic pyrazinoylguanidine sodium channel blockers)

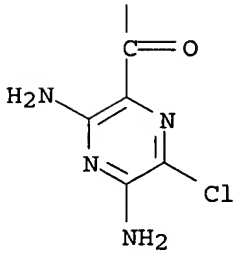
RN 845753-74-4 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-[4-[3-(2,4-dioxo-5-thiazolidinyl)propoxy]-1-piperidinyl]butyl]amino]iminomethyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



L148 ANSWER 7 OF 56 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:497502 CAPLUS
DOCUMENT NUMBER: 143:53440
TITLE: Substituted benzoimidazole compounds as transcription factor-modulating compounds useful as anti-infectives
INVENTOR(S): Levy, Stuart B.; Alekshun, Michael N.; Podlogar, Brent L.; Ohemeng, Kwasi; Verma, Atul K.; Warchol, Tadeusz; Bhatia, Beena; Bowser, Todd; Grier, Mark
PATENT ASSIGNEE(S): Paratek Pharmaceuticals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 463 pp., Cont.-in-part of U.S. Ser. No. 139,591.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005124678	A1	20050609	US 2003-700661		20031103
CA 2445515	AA	20021104	CA 2002-2445515		20020506
EP 1524974	A2	20050427	EP 2002-807554		20020506
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2005519998	T2	20050707	JP 2004-515557		20020506
US 2003229065	A1	20031211	US 2002-139591		20020814
US 2004106553	A1	20040603	US 2003-602562		20030624
PRIORITY APPLN. INFO.:			US 2001-288660P	P	20010504
			US 2002-139591	A2	20020814
			US 2002-423319P	P	20021101
			US 2002-425916P	P	20021113
			WO 2002-US14255	W	20020506
			US 2002-391345P	P	20020624
			US 2002-421218P	P	20021025
			US 2002-429142P	P	20021126
			US 2003-458935P	P	20030331

OTHER SOURCE(S): MARPAT 143:53440

AB Substituted benzoimidazole compds. useful as anti-infectives that decrease resistance, virulence, or growth of microbes are provided. Methods of making and using substituted benzoimidazole compds., as well as pharmaceutical prepns. thereof, in, e.g., reducing antibiotic resistance and inhibiting biofilms. The present invention identifies microbial transcription factors, especially transcription factors of the AraC-XylS family, as virulence factors in microbes and shows that inhibition of these factors reduces the virulence of microbial cells. Because these transcription factors control virulence, rather than essential cellular processes, the development of resistance is much less likely.

IC ICM A61K031-4184
INCL 514394000
CC 1-5 (Pharmacology)
Section cross-reference(s): 10, 28, 63
IT Acne
Cystic fibrosis
Osteomyelitis
(treatment of biofilms in; substituted benzoimidazole compds. as transcription factor-modulating compds. useful as anti-infectives)
IT 117-39-5 480-23-9 520-36-5 891-43-0 1218-82-2 1571-90-0
1645-21-2 1772-39-0 2513-33-9 2555-29-5 3164-28-1 3283-93-0
4143-63-9 4143-74-2 5211-78-9 5346-13-4 5452-31-3 5460-84-4
10066-15-6 10420-73-2 14172-90-8 14172-91-9 14172-92-0
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18706-63-3 22198-48-7 22395-22-8 22697-40-1 22894-67-3
25437-73-4 31283-09-7 32396-64-8 33289-14-4 36387-84-5
39679-60-2 39776-53-9 41383-95-3 41383-96-4 49619-82-1
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62536-78-1 63046-14-0 63576-07-8 65047-30-5 67574-58-7
70188-31-7 70591-05-8 71348-79-3 71720-87-1 76648-60-7
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300716-40-9 300723-23-3 300805-10-1 301354-45-0

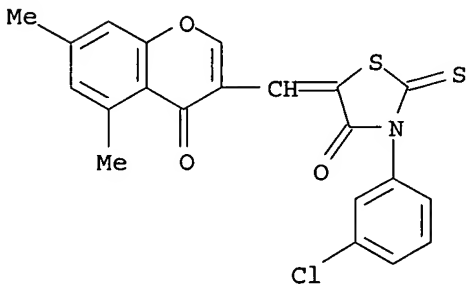
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(substituted benzoimidazole compds. as transcription factor-modulating compds. useful as anti-infectives)

IT **285987-31-7**

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(substituted benzoimidazole compds. as transcription factor-modulating compds. useful as anti-infectives)

RN 285987-31-7 CAPLUS

CN 4-Thiazolidinone, 3-(3-chlorophenyl)-5-[(5,7-dimethyl-4-oxo-4H-1-benzopyran-3-yl)methylene]-2-thioxo- (9CI) (CA INDEX NAME)



L148 ANSWER 8 OF 56 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:342583 CAPLUS
DOCUMENT NUMBER: 143:262072
TITLE: Activation of G551D-**CFTR** by bicyclooctane compounds is cAMP-dependent and exhibits low

sensitivity to thiazolidinone **CFTR** inhibitor **CFTRinh**-172

AUTHOR(S): Wang, Ying; Zhao, Lu; He, Cheng-yan; Xu, Li-na; Yang, Hong

CORPORATE SOURCE: Membrane Channel Research Laboratory, Northeast Normal University, Changchun, 130024, Peop. Rep. China

SOURCE: Chemical Research in Chinese Universities (2005), 21(2), 183-186
CODEN: CRCUED; ISSN: 1005-9040

PUBLISHER: Higher Education Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The G551D-**CFTR** mutation causing **cystic fibrosis** (CF) results from a missense mutation at codon 551 (G551D) in the gene encoding of the **cystic fibrosis** transmembrane conductance regulator (**CFTR**). The G551D mutation in **CFTR** results in a reduced functional channel but G551D-**CFTR** is appropriately inserted in the apical membrane. In previous studies we discovered a class of high-affinity bicyclooctane (BCO) G551D-**CFTR** activators (G551DBCOS) with Kd down to 1 μmol/L. In this study, we analyzed the pharmacol. activation of G551D-**CFTR** by the G551DBCOS by means of short circuit current anal. and cell-based fluorescence quenching assay. The G551DBCOS-induced G551D-**CFTR** activation is cAMP-dependent and is less sensitive to thiazolidinone **CFTR** inhibitor **CFTRinh**-172. These data suggest that (1) the phosphorylation of G551D-**CFTR** by protein kinase A is required for the activation by G551DBCOS; (2) G551DBCOS and **CFTRinh**-172 may act at the same site on the G551D-**CFTR** mol.

CC 6-3 (General Biochemistry)
Section cross-reference(s): 1, 13, 14

ST **cystic fibrosis** transmembrane conductance regulator mutant bicyclooctane activation cAMP; **CFTR** mutant G551D protein bicyclooctane binding partial inhibition thiazolidinone

IT Animal cell line
(FRT (Fischer rat thyroid); activation of G551D-**CFTR** by bicyclooctane compds. is cAMP-dependent and exhibits low sensitivity to thiazolidinone **CFTR** inhibitor **CFTRinh**-172)

IT Human
(activation of G551D-**CFTR** by bicyclooctane compds. is cAMP-dependent and exhibits low sensitivity to thiazolidinone **CFTR** inhibitor **CFTRinh**-172)

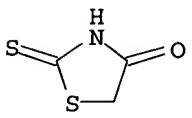
IT **CFTR** (**cystic fibrosis** transmembrane conductance regulator)
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(activation of G551D-**CFTR** by bicyclooctane compds. is cAMP-dependent and exhibits low sensitivity to thiazolidinone **CFTR** inhibitor **CFTRinh**-172)

IT Electric current
(biol.; activation of G551D-**CFTR** by bicyclooctane compds. is cAMP-dependent and exhibits low sensitivity to thiazolidinone **CFTR** inhibitor **CFTRinh**-172)

IT Biological transport
(efflux, channel-mediated; activation of G551D-**CFTR** by bicyclooctane compds. is cAMP-dependent and exhibits low sensitivity to thiazolidinone **CFTR** inhibitor **CFTRinh**-172)

IT Biological transport
(influx, channel-mediated; activation of G551D-**CFTR** by bicyclooctane compds. is cAMP-dependent and exhibits low sensitivity to thiazolidinone **CFTR** inhibitor **CFTRinh**-172)

IT Mutation
(missense, G551D; activation of G551D-**CFTR** by bicyclooctane compds. is cAMP-dependent and exhibits low sensitivity to thiazolidinone **CFTR** inhibitor **CFTRinh**-172)
IT 60-92-4, Cyclic AMP **141-84-4D**, derivs.
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(activation of G551D-**CFTR** by bicyclooctane compds. is cAMP-dependent and exhibits low sensitivity to thiazolidinone **CFTR** inhibitor **CFTRinh**-172)
IT 5721-34-6D, derivs.
RL: BSU (Biological study, unclassified); DMA (Drug mechanism of action); PAC (Pharmacological activity); BIOL (Biological study)
(activation of G551D-**CFTR** by bicyclooctane compds. is cAMP-dependent and exhibits low sensitivity to thiazolidinone **CFTR** inhibitor **CFTRinh**-172)
IT 7553-56-2, Iodine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(influx; activation of G551D-**CFTR** by bicyclooctane compds. is cAMP-dependent and exhibits low sensitivity to thiazolidinone **CFTR** inhibitor **CFTRinh**-172)
IT 56-84-8, L-Aspartic acid, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(residue 551; activation of G551D-**CFTR** by bicyclooctane compds. is cAMP-dependent and exhibits low sensitivity to thiazolidinone **CFTR** inhibitor **CFTRinh**-172)
IT 56-40-6, Glycine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(residue 551; activation of G551D-**CFTR** by bicyclooctane compds. is cAMP-dependent and exhibits low sensitivity to thiazolidinone **CFTR** inhibitor **CFTRinh**-172)
IT 7782-50-5, Chlorine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(transport; activation of G551D-**CFTR** by bicyclooctane compds. is cAMP-dependent and exhibits low sensitivity to thiazolidinone **CFTR** inhibitor **CFTRinh**-172)
IT **141-84-4D**, derivs.
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(activation of G551D-**CFTR** by bicyclooctane compds. is cAMP-dependent and exhibits low sensitivity to thiazolidinone **CFTR** inhibitor **CFTRinh**-172)
RN 141-84-4 CAPLUS
CN 4-Thiazolidinone, 2-thioxo- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L148 ANSWER 9 OF 56 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:995913 CAPLUS
DOCUMENT NUMBER: 141:420443
TITLE: **Cystic fibrosis** therapy with PPAR-γ inducers and antioxidants
INVENTOR(S): Freedman, Steven D.
PATENT ASSIGNEE(S): Beth Israel Deaconess Medical Center, USA

SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004098510	A2	20041118	WO 2004-US13412	20040430
WO 2004098510	A3	20050120		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-466672P P 20030430

AB This invention features methods for treating diseases associated with mutations in the **CFTR** gene by administering PPAR-γ inducers and/or antioxidants. Also disclosed are screening methods for identifying therapeutically useful candidate compds.

IC ICM A61K
CC 1-9 (Pharmacology)
Section cross-reference(s): 63
ST **cystic fibrosis** therapy **CFTR** gene PPAR gamma inducer antioxidant
IT Transcription factors
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AP-1 (activator protein 1), inhibitors; **cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**CFTR**; **cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)
IT Transcription factors
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NF-κB (nuclear factor of κ light chain gene enhancer in B-cells), inhibitors; **cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)
IT RNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(PPAR-γ; **cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)
IT Transcription factors
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(STAT (signal transducer and activator of transcription), inhibitors; **cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)
IT Biliary tract
(bile duct, cells; **cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)

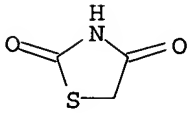
IT Intestine
Lung
(cells; **cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)
IT Lung, disease
(chronic obstructive pulmonary disease; **cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)
IT Vas deferens
(congenital bilateral absence of; **cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)
IT Antioxidants
Asthma
Cystic fibrosis
Drug screening
Gene therapy
Human
Macrophage
Pancreas
(**cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)
IT Spiro compounds
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)
IT Mutation
(in the **CFTR** gene; **cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)
IT Drug delivery systems
(inhalants; **cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)
IT Drug delivery systems
(injections, i.v.; **cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)
IT Inflammation
Pancreas, disease
(pancreatitis; **cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)
IT Biliary tract, disease
Inflammation
(sclerosing cholangitis; **cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)
IT Inflammation
Respiratory system, disease
(sinusitis, chronic; **cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)
IT Peroxisome proliferator-activated receptors
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(γ, inducers; **cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)
IT 154563-54-9
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(SP 100030; **cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)
IT 3483-12-3, Dithiothreitol 6892-68-8, Dithioerythritol 14844-07-6, Dithionite 23134-05-6, Pyrosulfite
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**cystic fibrosis** therapy with PPAR- inducers and antioxidants)

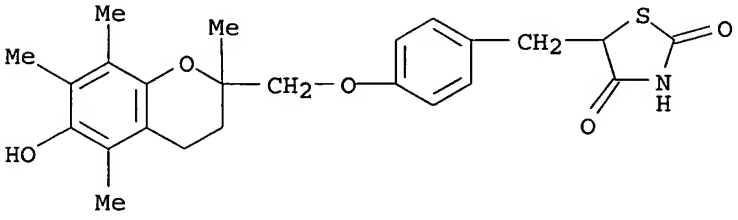
IT 50-81-7, Vitamin C, biological studies 52-90-4, Cysteine, biological studies 53-86-1, Indomethacin 87-17-2D, Salicylanilide, derivs. 129-56-6, SP600125 328-90-5, 2-Hydroxy-4-trifluoromethylbenzoic acid 328-90-5D, 2-Hydroxy-4-trifluoromethylbenzoic acid, derivs. 458-37-7, Curcumin 500-38-9, Nordihydroguaiaretic acid 891-60-1, Declopramide 1406-18-4, Vitamin E **2295-31-0D**, Thiazolidinedione, derivs. 7235-40-7, Beta-carotene 7782-49-2, Selenium, biological studies 10417-94-4, Eicosapentaenoic acid 15687-27-1, Ibuprofen 25769-03-3, 1-Pyrrolidinecarbodithioic acid 29679-58-1, Fenoprofen 29908-03-0 58186-27-9, Idebenone **97322-87-7**, Troglitazone **122320-73-4**, Rosiglitazone 160162-42-5 167869-21-8, PD98059 173026-17-0, BXT-51072 193295-10-2, STAT-induced STAT inhibitor 1 (mouse) 286465-43-8 286465-44-9 476198-73-9, Dexlipotam 796857-00-6, SSI 3 796857-01-7, SSI 2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)

IT **2295-31-0D**, Thiazolidinedione, derivs. **97322-87-7**, Troglitazone **122320-73-4**, Rosiglitazone
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**cystic fibrosis** therapy with PPAR-γ inducers and antioxidants)

RN 2295-31-0 CAPLUS
CN 2,4-Thiazolidinedione (8CI, 9CI) (CA INDEX NAME)

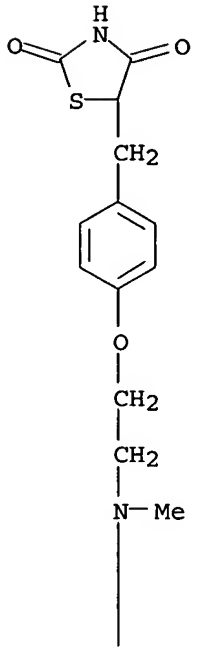


RN 97322-87-7 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

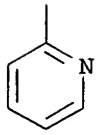


RN 122320-73-4 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



L148 ANSWER 10 OF 56 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:490736 CAPLUS
DOCUMENT NUMBER: 141:47336
TITLE: Combination treatment for diabetes and related diseases using exendins and thiazolidinediones
INVENTOR(S): Knudsen, Lotte Bjerre
PATENT ASSIGNEE(S): Novo Nordisk A/S, Den.
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004050115	A2	20040617	WO 2003-DK824	20031201
WO 2004050115	A3	20040722		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,

GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO,
NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ,
TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
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ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK,
TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1569682 A2 20050907 EP 2003-775117 20031201
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
US 2004180824 A1 20040916 US 2003-726734 20031203
PRIORITY APPLN. INFO.: DK 2002-1864 A 20021203
US 2002-431999P P 20021209
WO 2003-DK824 W 20031201

AB The invention provides methods for treatment and/or prevention of diabetes and diabetes-related diseases. More specifically, the methods and uses of the invention pertains to administration of an exendin-4 compound in combination with administration of a thiazolidinedione insulin sensitizer.

IC ICM A61K038-22
ICS A61K031-426; A61K031-427; A61P003-10

CC 1-10 (Pharmacology)

IT **Cystic fibrosis**
(diabetes related to; exendin-thiazolidinedione combination treatment for diabetes and related diseases)

IT **2295-31-0D**, Thiazolidinedione, derivs. 25322-68-3D, Polyethylene glycol, exendin-4 conjugates **74772-77-3**, Ciglitazone **97322-87-7**, Troglitazone **103926-56-3**, TZD300512 **109229-58-5**, Englitazone **111025-46-8**, Pioglitazone **118384-10-4**, T174 **122320-73-4**, Rosiglitazone **141200-24-0**, Darglitazone 141732-76-5, Exendin 4 **161600-01-7**, Isaglitazone **199113-98-9**, 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione 524675-01-2, CS 011 **705950-21-6**, CI 1037
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(exendin-thiazolidinedione combination treatment for diabetes and related diseases)

IT **2295-31-0D**, Thiazolidinedione, derivs. **74772-77-3**, Ciglitazone **97322-87-7**, Troglitazone **103926-56-3**, TZD300512 **109229-58-5**, Englitazone **111025-46-8**, Pioglitazone **118384-10-4**, T174 **122320-73-4**, Rosiglitazone **141200-24-0**, Darglitazone **161600-01-7**, Isaglitazone **199113-98-9**, 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione **705950-21-6**, CI 1037
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(exendin-thiazolidinedione combination treatment for diabetes and related diseases)

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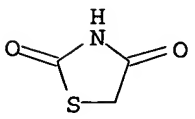
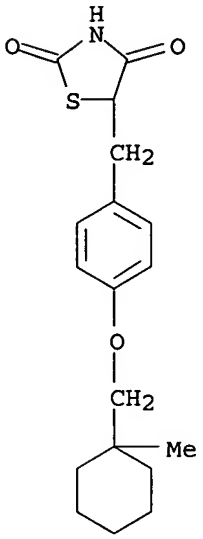
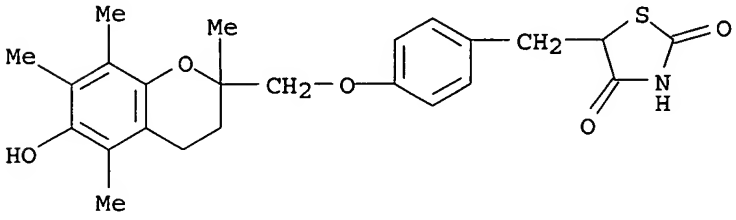


RN 74772-77-3 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[(1-methylcyclohexyl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 97322-87-7 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 103926-56-3 CAPLUS
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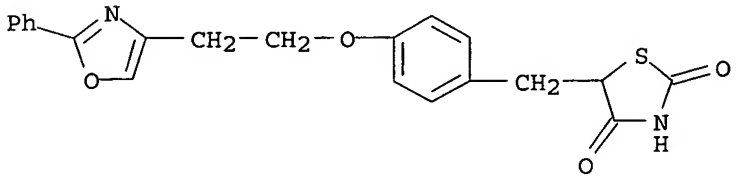

RN 109229-58-5 CAPLUS
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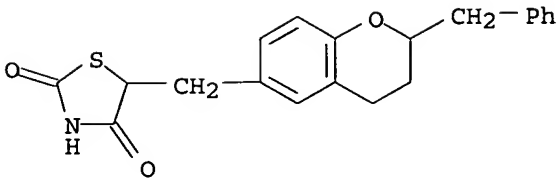
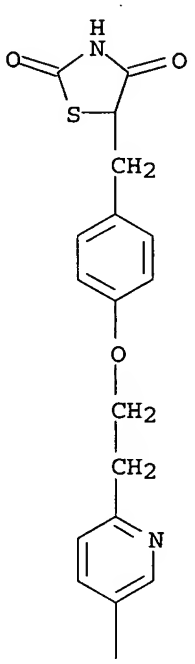


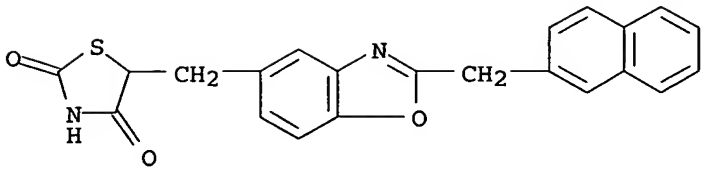
RN 111025-46-8 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-
(9CI) (CA INDEX NAME)

PAGE 1-A



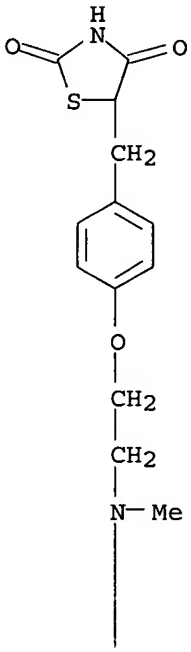
PAGE 2-A

RN 118384-10-4 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[2-(2-naphthalenylmethyl)-5-benzoxazolyl]methyl]-
(9CI) (CA INDEX NAME)

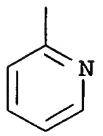


RN 122320-73-4 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

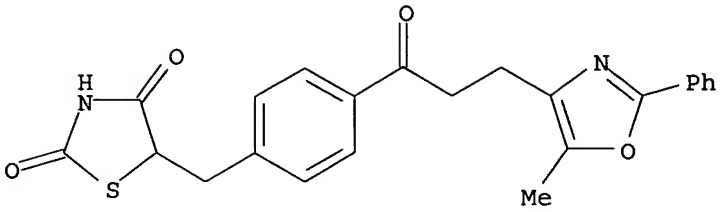
PAGE 1-A



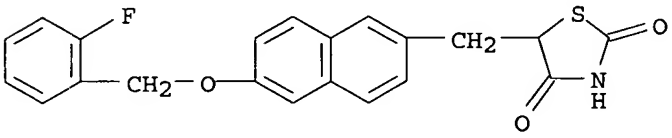
PAGE 2-A



RN 141200-24-0 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 161600-01-7 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[6-[(2-fluorophenyl)methoxy]-2-naphthalenyl]methyl]- (9CI) (CA INDEX NAME)



RN 199113-98-9 CAPLUS
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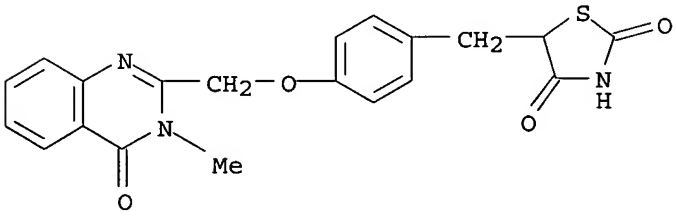
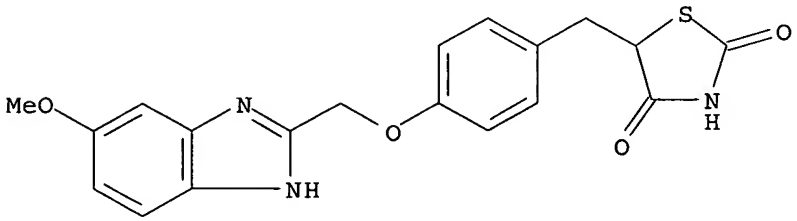


RN 705950-21-6 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[(5-methoxy-1H-benzimidazol-2-yl)methoxy]phenyl]methyl]-, monohydrochloride, (+)- (9CI) (CA INDEX NAME)

Rotation (+).
Currently available stereo shown.



● HCl

L148 ANSWER 11 OF 56 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:60341 CAPLUS
DOCUMENT NUMBER: 140:117406
TITLE: Liquid dosage compositions of stable nanoparticulate drugs
INVENTOR(S): Bosch, William H.; Hilborn, Matthew R.; Hovey, Douglas C.; Kline, Laura J.; Lee, Robert W.; Pruitt, John D.; Ryde, Niels P.; Ryde, Tuula A.; Xu, Shuqian
PATENT ASSIGNEE(S): Elan Pharma International, Ltd, Ire.
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 16
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004006959	A1	20040122	WO 2003-US22187	20030716
WO 2004006959	C1	20050331		
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2492488	AA	20040122	CA 2003-2492488	20030716
EP 1551457	A1	20050713	EP 2003-764723	20030716
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JP 2005536512	T2	20051202	JP 2004-521891	20030716
PRIORITY APPLN. INFO.:			US 2002-396530P P	20020716
			WO 2003-US22187 W	20030716

AB The present invention relates to liquid dosage compns. of stable nanoparticulate drugs. The liquid dosage compns. of the invention include osmotically active crystal growth inhibitors that stabilize the nanoparticulate active agents against crystal and particle size growth of the drug. Thus, an aqueous nanoparticulate colloidal dispersion (NCD) comprising drug 32.5 Copovidone 6.5, and dioctyl sodium sulfosuccinate 0.464% by weight was prepared by milling for 3.8 h under high energy milling conditions. The final mean particle size (by weight) of the drug particles was 161 nm. The concentrated NCD was then diluted with preserved water and glycerol (the osmotically active crystal growth inhibitor) to 0.5-3.0% drug.

IC ICM A61K047-02
ICS A61K047-10; A61K047-26; A61K009-10; A61K009-14; A61K031-192; A61K031-58
CC 63-6 (Pharmaceuticals)
IT AIDS (disease)
Acne
Adrenoceptor agonists
Allergy
Allergy inhibitors
Aloe barbadensis
Alzheimer's disease
Analgesics

Anorexia
Anthelmintics
Anti-AIDS agents
Anti-Alzheimer's agents
Anti-inflammatory agents
Antiarrhythmics
Antiarthritics
Antiasthmatics
Antibacterial agents
Antibiotics
Anticoagulants
Anticonvulsants
Antidepressants
Antidiabetic agents
Antiemetics
Antihistamines
Antihypertensives
Antimigraine agents
Antiobesity agents
Antioxidants
Antirheumatic agents
Antitumor agents
Antitussives
Antiviral agents
Anxiety
Anxiolytics
Arthritis
Asthma
Blood products
Blood substitutes
Cachexia
Cardiovascular agents
Cardiovascular system, disease
Castration
Cholinergic agonists
Commiphora mukul
Cough
  Cystic fibrosis
Diabetes mellitus
Diuresis
Diuretics
Dopamine agonists
Drug bioavailability
Drug bioequivalence
Dysmenorrhea
Dyspepsia
Emphysema
Epilepsy
Fish
Food
Food additives
Food poisoning
Fungicides
Gout
Hemorrhage
Hemostatics
Herb
Hirsutism
Hormone replacement therapy
Human

Hypertension
Hypnotics and Sedatives
Imaging agents
Immunosuppressants
Immunosuppression
Inflammation
Inotropics
Kidney, disease
Kidney, neoplasm
Mammary gland, neoplasm
Motion sickness
Muscarinic antagonists
Muscle contraction
Muscle relaxants
Neoplasm
Obesity
Osteoarthritis
Osteoporosis
Pain
Parathyroid gland
Particle size distribution
Prostate gland, neoplasm
Radiopharmaceuticals
Respiratory distress syndrome
Rheumatoid arthritis
Shear
Size reduction
Sleep
Solubility
Stabilizing agents
Storage
Thrombosis
Transplant and Transplantation
Transplant rejection
Uterus, neoplasm
Vasodilation
Vasodilators
Viscosity
Vomiting
(liquid dosage compns. of stable nanoparticulate drugs)

IT 50-35-1, Thalidomide 50-44-2, Mercaptopurine 50-53-3, Chlorpromazine, biological studies 50-78-2, Acetylsalicylic acid 50-99-7, Glucose, biological studies 52-53-9, Verapamil 56-81-5, Glycerol, biological studies 56-85-9, Glutamine, biological studies 57-09-0, Hexadecyltrimethylammonium bromide 57-11-4, Stearic acid, biological studies 57-48-7, Fructose, biological studies 57-50-1, Sucrose, biological studies 57-55-6, Propylene glycol, biological studies 57-88-5, Cholesterol, biological studies 58-32-2, Dipyridamole 59-30-3, Folic acid, biological studies 62-49-7D, Choline, esters 63-42-3, Lactose 64-17-5, Ethanol, biological studies 67-45-8, Furazolidone 69-65-8, Mannitol 69-89-6D, Xanthine, derivs. 73-31-4, Melatonin 75-65-0, biological studies 80-74-0, Acetylsulfisoxazole 87-99-0, Xylitol 99-20-7, Trehalose 102-71-6, Triethanolamine, biological studies 110-86-1D, Pyridine, quaternized, salts 112-00-5, Lauryltrimethylammonium chloride 123-03-5, CPC 129-03-3, Cyproheptadine 132-17-2, Benztropine mesylate 134-32-7D, 1-Naphthylamine, alkyldimethylammonium salts 139-07-1, Lauryldimethylbenzylammonium chloride 140-72-7, Cetylpyridinium bromide 143-67-9, Vinblastine sulfate 148-79-8, Thiabendazole 151-21-3, SDS, biological studies 154-42-7, Thioguanine 288-32-4D, Imidazole,

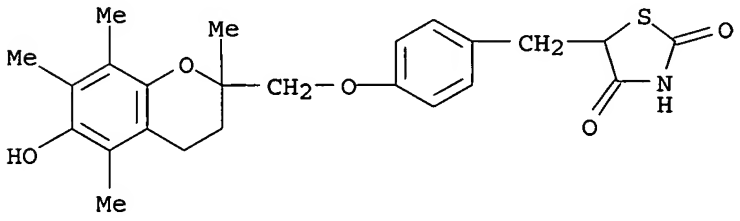
quaternized, salts 303-53-7, Cyclobenzaprine 396-01-0, Triamterene 500-92-5, Proguanil 502-65-8, Lycopene 645-05-6, Altretamine 846-50-4, Temazepam 1119-94-4, Dodecyltrimethylammonium bromide 1119-97-7, Tetradecyltrimethylammonium bromide 1200-22-2, Lipoic acid 1327-43-1, Magnesium aluminum silicate 1592-23-0, Calcium Stearate 1643-19-2, Tetrabutylammonium bromide 1951-25-3, Amiodarone 1977-10-2, Loxapine 2062-78-4, Pimozide 2082-84-0, Decyltrimethylammonium bromide 2609-46-3, Amiloride 3416-24-8, Glucosamine 3458-28-4, Mannose 4205-90-7, Clonidine 4342-03-4, Dacarbazine 5137-55-3, Methyltrioctylammonium chloride 5350-41-4, Benzyltrimethylammonium bromide 7173-51-5, Dimethyldidecylammonium chloride 7281-04-1, Lauryldimethylbenzylammonium bromide 7447-40-7, Potassium chloride (KCl), biological studies 7647-14-5, Sodium chloride, biological studies 7786-30-3, Magnesium chloride (MgCl2), biological studies 9000-01-5, Gum acacia 9000-30-0D, Guar gum, cationic derivs. 9000-65-1, Tragacanth gum 9001-63-2, Lysozyme 9002-89-5, Poly(vinyl alcohol) 9003-39-8, Polyvinylpyrrolidone 9004-32-4 9004-34-6, Cellulose, biological studies 9004-54-0, Dextran, biological studies 9004-62-0, Hydroxyethyl cellulose 9004-64-2, Hydroxypropyl cellulose 9004-65-3, Hypromellose 9004-67-5, Methyl cellulose 9004-99-3, Polyethylene glycol stearate 9005-32-7, Alginic acid 9007-12-9, Calcitonin 9007-27-6, Chondroitin 9011-14-7, Poly(methyl methacrylate) 9011-14-7D, Poly(methyl methacrylate), hydrolyzed, trimethylammonium salts 9050-04-8, Cellulose, carboxymethyl ether, calcium salt 9050-31-1, Hydroxypropyl methyl cellulose phthalate 10118-90-8, Minocycline 12441-09-7D, Sorbitan, esters 13292-46-1, Rifampin 16679-58-6, Desmopressin 18186-71-5, Dodecyltriethylammonium bromide 24280-93-1 25086-89-9, Vinyl acetate-1-vinyl-2-pyrrolidone copolymer 25301-02-4, Ethylene oxide-formaldehyde-4-(1,1,3,3-Tetramethylbutyl)phenol copolymer 25322-68-3, Polyethylene glycol 25322-68-3D, Polyethylene glycol, phospholipid derivs. 26062-79-3, Poly(diallyldimethylammonium chloride) 27195-16-0, Sucrose distearate 27321-96-6, Polyethylene glycol cholesteryl ether 28228-56-0 28679-24-5, Dodecylbenzyltriethylammonium chloride 28981-97-7, Alprazolam 29094-61-9, Glipizide 29767-20-2, Teniposide 29836-26-8, n-Octyl-β-D-glucopyranoside 31431-39-7, Mebendazole 31566-31-1, Glyceryl monostearate 33419-42-0, Etoposide 34911-55-2, Bupropion 36735-22-5, Quazepam 37318-31-3, Sucrose stearate 38443-60-6, Decyltriethylammonium chloride 39809-25-1, Penciclovir 42399-41-7, Diltiazem 51264-14-3, Amsacrine 51569-39-2, Olin 10G 52128-35-5, Trimetrexate 52467-63-7, Tricetylmethylammonium chloride 55008-57-6 55268-75-2, Cefuroxime 55348-40-8, Triton X-200 58846-77-8, n-Decyl β-D-glucopyranoside 59080-45-4, n-Hexyl β-D-glucopyranoside 59122-55-3, n-DoDecyl β-D-glucopyranoside 59277-89-3, Acyclovir 65271-80-9, Mitoxantrone 65277-42-1, Ketoconazole 66085-59-4, Nimodipine 69227-93-6, n-DoDecyl β-D-maltoside 69984-73-2, n-Nonyl β-D-glucopyranoside 70458-96-7, Norfloxacin 72509-76-3, Felodipine 72558-82-8, Ceftazidime 72559-06-9, Rifabutin 73590-58-6, Omeprazole 76095-16-4, Enalapril maleate 76420-72-9, Enalaprilat 76824-35-6, Famotidine 78617-12-6, n-Heptyl β-D-glucopyranoside 79617-96-2, Sertraline 79794-75-5, Loratadine 81098-60-4, Cisapride 81103-11-9, Clarithromycin 81409-90-7, Cabergoline 81859-24-7, Polyquat 10 82494-09-5, n-Decyl β-D-maltoside 84449-90-1, Raloxifene 85261-19-4, Nonanoyl-N-methylglucamide 85261-20-7, Decanoyl-N-methylglucamide 85316-98-9 85618-20-8, n-Heptyl β-D-thioglucopyranoside 85618-21-9, n-Octyl-β-D-thioglucopyranoside 85721-33-1, Ciprofloxacin 86386-73-4, Fluconazole 87679-37-6, Trandolapril 91161-71-6, Terbinafine 95233-18-4, Atovaquone **97322-87-7**, Troglitazone 100286-97-3, Milrinone lactate 101397-87-9, D-Glucitol, 1-deoxy-1-[methyl(1-oxoheptyl)amino]- 103577-45-3, Lansoprazole

104987-11-3, Tacrolimus 106266-06-2, Risperidone 106392-12-5, Pluronic
107397-59-1, Tetronic 150R8 110617-70-4, Poloxamine 113665-84-2,
Clopidogrel 115956-12-2, Dolasetron 127666-00-6 127779-20-8,
Saquinavir 132539-06-1, Olanzapine 136817-59-9, Delavirdine
138402-11-6, Irbesartan 139481-59-7, Candesartan 139755-83-2,
Sildenafil 144034-80-0, Rizatriptan 145599-86-6, Cerivastatin
147059-72-1, Trovafloxacin 159989-65-8, Nelfinavir mesylate
283158-20-3 329326-68-3, p-Isononylphenoxypolyglycidol 503178-50-5
608094-65-1, PEG-vitamin A 630400-66-7 630400-67-8 634601-99-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(liquid dosage compns. of stable nanoparticulate drugs)

IT **97322-87-7**, Troglitazone
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(liquid dosage compns. of stable nanoparticulate drugs)

RN 97322-87-7 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L148 ANSWER 12 OF 56 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:182242 CAPLUS
DOCUMENT NUMBER: 140:223260
TITLE: Treatment and prevention of abnormal scar formation in keloids and other cutaneous or internal wounds or lesions
INVENTOR(S): Tuan, Tai-lan; Benya, Paul D.; Warburton, David
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 26 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004043026	A1	20040304	US 2003-439267	20030513
WO 2004041155	A2	20040521	WO 2003-US15548	20030513
WO 2004041155	A3	20040923		

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,

FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
EP 1509236 A2 20050302 EP 2003-808378 20030513
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
BR 2003011172 A 20050426 BR 2003-11172 20030513
PRIORITY APPLN. INFO.: US 2002-380696P P 20020513
WO 2003-US15548 W 20030513

AB The present invention relates to findings that reducing the activity of Plasminogen Activator Inhibitor-1 (PAI-1) suppresses an excessive deposition of collagen which is known as a cause for the formation of abnormal scars. These abnormal scars include but are not limited to keloids, adhesions, hypertrophic scars, skin disfiguring conditions, fibrosis, fibrocystic conditions, contractures, and scleroderma, all of which are associated with or caused by an excessive deposit of collagen in a wound healing process. Accordingly, aspects of the present invention are directed to the reduction of PAI-1 activity to decrease an excessive accumulation of collagen, prevent the formation of an abnormal scar, and/or treat abnormal scars that result from an excessive accumulation of collagen. The PAI-1 activity can be reduced by PAI-1 inhibitors which include but are not limited to PAI-1 neutralizing antibodies, diketopiperazine based compds., tetramic acid based compds., hydroxyquinolinone based compds., Enalapril, Eprosartan, Troglitazone, Vitamin C, Vitamin E, Mifepristone (RU486), and Spironolactone to name a few. Another aspect of the present invention is directed to methods of measuring PAI-1 activity in a wound healing process and determining the propensity of the formation of an abnormal scar.

IC ICM A61K039-395
ICS A61K038-05; A61K031-58; A61K031-56; A61K031-495; A61K031-355; A61K031-401

INCL 424146100; 514174000; 514179000; 514423000; 514018000; 514458000; 514474000; 514255020; 514560000; 514312000

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1, 14, 15

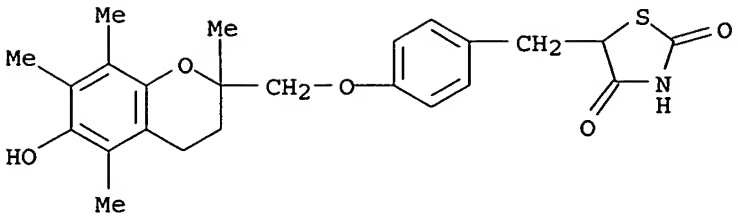
IT **Cystic fibrosis**
Fibrosis
Keloid
Wound healing
Wound healing promoters
(prevention of abnormal scar formation in keloids and other cutaneous or internal wounds or lesions)

IT 50-81-7, Vitamin c, biological studies 52-01-7, Spironolactone 106-57-0D, Diketopiperazine, derivs. 503-83-3D, Tetramic acid, derivs. 1406-18-4, Vitamin e 62571-86-2, Captopril 75847-73-3, Enalapril 82834-16-0, Perindopril 84371-65-3, Mifepristone 89371-37-9, Imidapril **97322-87-7**, Troglitazone 98048-97-6, Fosinopril 104534-80-7D, Quinolinone, hydroxy derivs. 133040-01-4, Eprosartan 133240-46-7, l158809 223754-54-9
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prevention of abnormal scar formation in keloids and other cutaneous or internal wounds or lesions)

IT **97322-87-7**, Troglitazone
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prevention of abnormal scar formation in keloids and other cutaneous or internal wounds or lesions)

RN 97322-87-7 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



L148 ANSWER 13 OF 56 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:154224 CAPLUS
DOCUMENT NUMBER: 138:193294
TITLE: Expandable gastric retention device containing pharmaceutical compositions
INVENTOR(S): Ayres, James W.
PATENT ASSIGNEE(S): The State of Oregon Acting by and Through the State Board of Higher Education On Behalf of Oregon State University, USA
SOURCE: PCT Int. Appl., 110 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003015745	A1	20030227	WO 2001-US46146	20011022
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2456976	AA	20030227	CA 2001-2456976	20011022
EP 1416914	A1	20040512	EP 2001-995328	20011022
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001017123	A	20040928	BR 2001-17123	20011022
CN 1543337	A	20041103	CN 2001-823544	20011022
JP 2005501097	T2	20050113	JP 2003-520705	20011022
NO 2004000611	A	20040416	NO 2004-611	20040211
US 2004219186	A1	20041104	US 2004-778917	20040213
ZA 2004002066	A	20050509	ZA 2004-2066	20040315
PRIORITY APPLN. INFO.:			US 2001-313078P	P 20010816
			WO 2001-US46146	W 20011022

AB The present application concerns gastric retention devices formed from compns. comprising polymeric materials, such as polysaccharides, and optional addnl. materials including excipients, therapeutics, and diagnostics, that reside in the stomach for a controlled and prolonged period of time. Dry powders of xanthan gum and locust bean gum were mixed intimately were converted to dried films. The dried films were compressed with the help of specially made punches and dies. A series of dies with

decreasingly narrow internal diams. were used. A punch pushes the film from one die into the next die, followed by pushing of the film by another punch into the next die. This process takes place in succession until a point is reached where the film is small enough to put into a desired capsule size.

IC ICM A61K009-00
ICS A61K009-20; A61K047-36

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

IT Adrenoceptor agonists
Adrenoceptor antagonists
Analgesics
Anesthetics
Antacids
Anti-AIDS agents
Anti-Alzheimer's agents
Anti-infective agents
Antiarrhythmics
Antibiotics
Anticonvulsants
Antidepressants
Antidiabetic agents
Antidotes
Antiemetics
Antihistamines
Antihypertensives
Antimicrobial agents
Antimigraine agents
Antiobesity agents
Antiparkinsonian agents
Antipsychotics
Antirheumatic agents
Antitumor agents
Appetite depressants
Cardiovascular agents
Cholinergic agonists
Cholinergic antagonists
Contraceptives
Cystic fibrosis
Deodorants (personal)
Digestive tract
Dissolution
Diuretics
Dizziness
Dopamine agonists
Drug bioavailability
Fungicides
Gastric juice
Human
Hypnotics and Sedatives
Imaging agents
Immunomodulators
Immunosuppressants
Intestinal juice
Ion exchangers
Medical goods
Muscle relaxants
Nervous system stimulants
Plasticizers
Psychotropics

Stomach
Urinary system
Vagina
Vasodilators
Wilson's disease
(expandable gastric retention device containing pharmaceutical compns.)

IT 50-44-2, Mercaptopurine 50-53-3, Chlorpromazine, biological studies 51-63-8, Dextroamphetamine sulfate 52-01-7, Spironolactone 54-31-9, Furosemide 58-14-0, Pyrimethamine 58-38-8, Prochlorperazine 59-66-5, Acetazolamide 63-89-8, Colfosceril palmitate 71-27-2, Succinylcholine chloride 89-57-6, Mesalazine 148-82-3, Melphalan 154-42-7, Thioguanine 305-03-3, Chlorambucil 315-30-0, Allopurinol 396-01-0, Triamterene 440-17-5, Trifluoperazine hydrochloride 554-13-2, Lithium carbonate 637-32-1, Proguanil hydrochloride 813-93-4, Bismuth citrate 1508-76-5, Procyclidine hydrochloride 2152-44-5, Betamethasone valerate 5534-09-8, Beclomethasone dipropionate 8064-90-2, Co-trimoxazole 9000-40-2, Locust bean gum 9004-65-3, HPMC 11138-66-2, Xanthan gum 12650-69-0, Mupirocin 13492-01-8, Tranylcypromine sulfate 18559-94-9, Albuterol 20830-75-5, Digoxin 25122-46-7, Clobetasol propionate 25953-19-9, Cefazolin 26787-78-0, Amoxicillin 29457-07-6, Ticarcillin disodium 30516-87-1, Zidovudine 31677-93-7, Bupropion hydrochloride 35121-78-9, Epoprostenol 42924-53-8, Nabumetone 51481-61-9, Cimetidine 54965-21-8, Albendazole 55268-75-2, Cefuroxime 59277-89-3, Acyclovir 61177-45-5, Clavulanate potassium 61336-70-7, Amoxicillin trihydrate 64211-46-7, Oxiconazole nitrate 64228-81-5, Atracurium besylate 66357-35-5, Ranitidine 66357-59-3, Ranitidine hydrochloride 70059-30-2, Cimetidine hydrochloride 71486-22-1, Vinorelbine 72558-82-8, Ceftazidime 72956-09-3, Carvedilol 73590-58-6, Omeprazole 76095-16-4, Enalapril maleate 78246-49-8, Paroxetine hydrochloride 79902-63-9, Simvastatin 80474-14-2, Fluticasone propionate 84057-84-1, Lamotrigine 89365-50-4, Salmeterol 91374-20-8, Ropinirole hydrochloride 94749-08-3, Salmeterol xinafoate 95233-18-4, Atovaquone 96946-42-8, Cisatracurium besylate 99614-01-4, Ondansetron hydrochloride 103628-46-2, Sumatriptan 119413-54-6, Topotecan hydrochloride 121679-13-8, Naratriptan 124750-99-8, Losartan potassium 124832-27-5, Valacyclovir hydrochloride 134678-17-4, Lamivudine 139110-80-8, Zanamivir 142373-60-2, Tirofiban hydrochloride **155141-29-0**, Rosiglitazone maleate 161814-49-9, Amprenavir 161973-10-0, Esomeprazole magnesium 162011-90-7, Rofecoxib 179463-17-3, Caspofungin acetate 188062-50-2, Abacavir sulfate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(expandable gastric retention device containing pharmaceutical compns.)

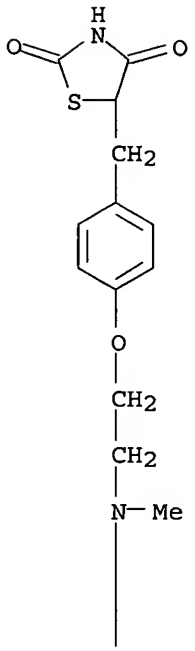
IT **155141-29-0**, Rosiglitazone maleate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(expandable gastric retention device containing pharmaceutical compns.)

RN 155141-29-0 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

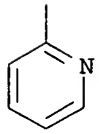
CM 1

CRN 122320-73-4
CMF C18 H19 N3 O3 S

PAGE 1-A



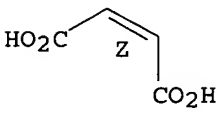
PAGE 2-A



CM 2

CRN 110-16-7
CMF C4 H4 O4

Double bond geometry as shown.



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L148 ANSWER 14 OF 56 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:971725 CAPLUS
DOCUMENT NUMBER: 140:35893
TITLE: Transcription factor modulating compounds and methods

of use thereof
INVENTOR(S): Levy, Stuart B.; Alekshun, Michael N.; Podlogar, Brent L.; Ohemeng, Kwasi; Verma, Atul K.; Warchol, Tadeusz; Bhatia, Beena
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 301 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003229065	A1	20031211	US 2002-139591	20020814
CA 2445515	AA	20021104	CA 2002-2445515	20020506
WO 2004001058	A2	20031231	WO 2002-US14255	20020506
WO 2004001058	A3	20050303		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
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R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2005519998	T2	20050707	JP 2004-515557	20020506
US 2005124678	A1	20050609	US 2003-700661	20031103

PRIORITY APPLN. INFO.:

US 2001-288660P	P	20010504
WO 2002-US14255	W	20020506
US 2002-139591	A2	20020814
US 2002-423319P	P	20021101
US 2002-425916P	P	20021113

OTHER SOURCE(S): MARPAT 140:35893

AB Methods for identifying compound useful as anti-infectives that decrease resistance, virulence, or growth of microbes are provided. In one embodiment, the method comprises contacting a microbial cell comprising: (1) a selectable marker under the control of a transcription factor responsive element and (2) a transcription factor, with a compound under conditions which allow interaction of the compound with the microbial cell; and measuring the ability of the compound to affect the growth or survival of the microbial cell as an indication of whether the test compound modulates the activity of a transcription factor.

IC ICM A61K031-555
ICS A61K031-505; A61K031-4745; A61K031-47; A61K031-415; A61K031-40; A61K031-407
INCL 514185000; 514256000; 514311000; 514303000; 514383000; 514381000; 514394000; 514410000; 514408000
CC 1-5 (Pharmacology)
Section cross-reference(s): 10, 28, 63
IT Acne
Cystic fibrosis
Immunodeficiency
Osteomyelitis
(biofilm infection, treatment; transcription factor modulating compds.

as anti-infectives agents that decrease resistance and virulence and growth identified by determining marker under control of responsive element)

IT 51-17-2D, Benzimidazole, derivs. 91-22-5D, Quinoline, derivs. 110-86-1D, Pyridine, derivs. 117-39-5 123-75-1D, Pyrrolidine, derivs. 288-94-8D, 1H-Tetrazole, derivs. 289-95-2D, Pyrimidine, derivs. 480-23-9 520-36-5 891-43-0 1218-82-2 1571-85-3 1571-90-0 1645-21-2 1772-39-0 2513-33-9 2555-29-5 3164-28-1 3283-93-0 4143-63-9 4143-74-2 5211-78-9 5346-13-4 5452-31-3 5460-84-4 10066-15-6 10420-73-2 14172-90-8 14172-91-9 14172-92-0 14244-55-4 14514-68-2 14518-23-1 16796-31-9 18384-19-5 18706-63-3 22198-48-7 22395-22-8 22697-40-1 22894-67-3 25437-73-4 31283-09-7 32396-64-8 33289-14-4 36387-84-5 37306-44-8D, Triazole, derivs. 39679-60-2 39776-53-9 41383-95-3 41383-96-4 49619-82-1 50287-25-7 50878-11-0 55736-01-1 57645-95-1 58996-65-9 62536-78-1 63046-14-0 63576-07-8 65047-30-5 67574-57-6 67574-58-7 70188-31-7 70591-05-8 71348-79-3 71720-87-1 76648-60-7 79049-98-2 84437-40-1 88379-74-2 89002-85-7 89813-65-0 91352-96-4 91486-87-2 92301-83-2 92831-11-3 92897-45-5 95356-81-3 95594-15-3 95716-70-4 96754-58-4 103855-21-6 104676-23-5 106726-42-5 107607-43-2 107792-87-0 109211-66-7 109723-54-8 110442-19-8 116718-53-7 126145-51-5 129415-03-8 129718-80-5 129886-25-5 129886-26-6 138884-21-6 138915-42-1 140410-61-3 146618-32-8 154269-13-3 154546-75-5 154678-99-6 154867-12-6 155276-97-4 156172-93-9 157428-39-2 157428-40-5 158584-21-5 159325-85-6 161466-04-2 164355-99-1 164356-03-0 167493-42-7 168209-86-7 175136-52-4 177082-78-9 177082-79-0 177082-84-7 182171-05-7 210639-69-3 210639-84-2 214140-91-7 216382-88-6D, Imidazopyridine, derivs. 216880-62-5 221179-01-7 222715-96-0 222716-13-4 222716-32-7 231630-20-9 232927-14-9 248595-25-7 252331-98-9 253178-59-5 254980-04-6 254980-06-8 254980-08-0 255395-82-5 255714-31-9 255725-40-7 256347-92-9 256417-22-8 256488-11-6 256488-13-8 256521-48-9 257861-94-2 257869-87-7 261946-03-6 261946-04-7 261946-06-9 262856-10-0 262856-11-1 262856-14-4 262856-15-5 263016-22-4 263016-25-7 263744-91-8 263766-87-6 263766-88-7 263766-94-5 263766-96-7 264232-74-8 264626-20-2 264626-22-4 265130-20-9 266362-06-5 266362-07-6 266362-08-7 266362-72-5 271775-19-0 279691-70-2 282523-56-2 282523-61-9 285980-79-2 285985-78-6 285985-96-8 **285987-31-7** 286439-77-8 289651-63-4 289651-74-7 289651-75-8 292170-06-0 292640-33-6 292641-43-1 292641-59-9 292641-66-8 292641-77-1 292641-89-5 292641-94-2 292641-96-4 292870-96-3 292871-13-7 292871-19-3 292871-23-9 292871-24-0 292871-26-2 292871-48-8 292871-52-4 292871-54-6 292871-55-7 292871-65-9 292871-69-3 292871-78-4 292871-81-9 292871-86-4 292871-94-4 292871-99-9 292872-04-9 292872-05-0 292872-11-8 292872-14-1 292875-92-4 292876-62-1 292877-08-8 292877-14-6 292877-44-2 293760-39-1 293760-44-8 294873-89-5 295787-47-2 296772-03-7 296790-72-2 296790-73-3 296790-75-5 296790-77-7 296791-26-9 296791-46-3 296791-48-5 296791-57-6 296793-15-2 296885-59-1 299198-34-8 299921-77-0 299964-86-6 300360-28-5 300377-27-9 300377-30-4

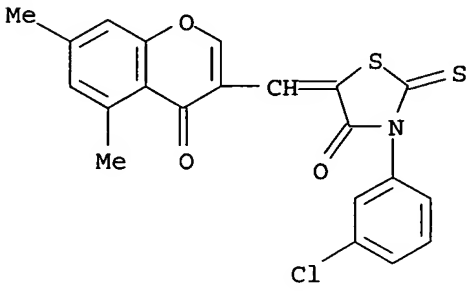
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(transcription factor modulating compds. as anti-infectives agents that decrease resistance and virulence and growth identified by determining marker under control of responsive element)

IT **285987-31-7**

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(transcription factor modulating compds. as anti-infectives agents that decrease resistance and virulence and growth identified by determining marker
under control of responsive element)
RN 285987-31-7 CAPLUS
CN 4-Thiazolidinone, 3-(3-chlorophenyl)-5-[(5,7-dimethyl-4-oxo-4H-1-benzopyran-3-yl)methylene]-2-thioxo- (9CI) (CA INDEX NAME)



L148 ANSWER 15 OF 56 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:338762 CAPLUS
DOCUMENT NUMBER: 134:362292
TITLE: Methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile
INVENTOR(S): Farr, Spencer
PATENT ASSIGNEE(S): Phase-1 Molecular Toxicology, USA
SOURCE: PCT Int. Appl., 222 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032928	A2	20010510	WO 2000-US30474	20001103
WO 2001032928	A3	20020725		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-165398P P 19991105
US 2000-196571P P 20000411

AB The invention discloses methods, gene databases, gene arrays, protein arrays, and devices that may be used to determine the hypersensitivity of individuals to a given agent, such as drug or other chemical, in order to prevent toxic side effects. In one embodiment, methods of identifying hypersensitivity in a subject by obtaining a gene expression profile of multiple genes associated with hypersensitivity of the subject suspected to be hypersensitive, and identifying in the gene expression profile of the subject a pattern of gene expression of the genes associated with hypersensitivity are disclosed. The gene expression profile of the

subject may be compared with the gene expression profile of a normal individual and a hypersensitive individual. The gene expression profile of the subject that is obtained may comprise a profile of levels of mRNA or cDNA. The gene expression profile may be obtained by using an array of nucleic acid probes for the plurality of genes associated with hypersensitivity. The expression of the genes predetd. to be associated with hypersensitivity is directly related to prevention or repair of toxic damage at the tissue, organ or system level. Gene databases arrays and apparatus useful for identifying hypersensitivity in a subject are also disclosed.

IC ICM C12Q001-68
ICS G01N033-50

CC 3-4 (Biochemical Genetics)
Section cross-reference(s): 1, 6, 7, 13, 15

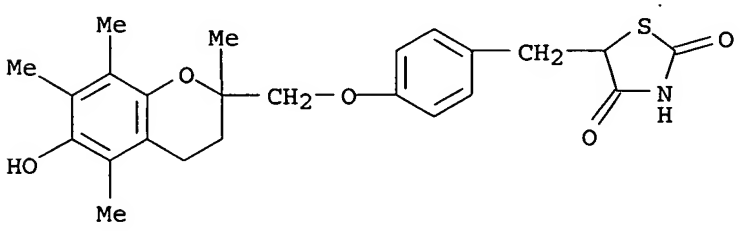
IT **CFTR** (**cystic fibrosis** transmembrane conductance regulator)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 92665-29-7, Cefprozil 93390-81-9, Fosphenytoin 93413-69-5, Venlafaxine 93479-97-1, Glimepiride 93957-54-1, Fluvastatin 95058-81-4, Gemcitabine 95233-18-4, Atovaquone 96036-03-2, Meropenem **97322-87-7**, Troglitazone 97519-39-6, Ceftibuten 97534-21-9, Merbarone 97682-44-5, Irinotecan 98048-97-6, Fosinopril 98319-26-7, Finasteride 100986-85-4, Levofloxacin 102767-28-2, Levetiracetam 103577-45-3, Lansoprazole 103628-46-2, Sumatriptan 104227-87-4, Famciclovir 104632-26-0, Pramipexole 105102-22-5, Mometasone 105462-24-6 105857-23-6, Alteplase 106133-20-4, Tamsulosin 106266-06-2, Risperidone 106392-12-5, Poloxamer 188 106650-56-0, Sibutramine 107753-78-6, Zafirlukast 107868-30-4, Exemestane 109889-09-0, Granisetron **111025-46-8**, Pioglitazone 112809-51-5, Letrozole 112965-21-6, Calcipotriene 114798-26-4, Losartan 115103-54-3, Tiagabine 115956-13-3, Dolasetron mesylate 116644-53-2, Mibefradil 117976-89-3, Rabeprazole 119383-00-5 119914-60-2, Grepafloxacin 120014-06-4, Donepezil 121679-13-8, Naratriptan **122320-73-4**, Rosiglitazone 122647-32-9, Ibutilide fumarate 122852-42-0, Alosetron 123948-87-8, Topotecan 124937-51-5, Tolterodine 126040-58-2, Calcium polycarbophil 127779-20-8, Saquinavir 129311-55-3, Ganirelix acetate 129318-43-0, Alendronate sodium 129618-40-2, Navirapine 130209-82-4, Latanoprost 130929-57-6, Entacapone 134308-13-7, Tolcapone 134523-00-5, Atorvastatin 137862-53-4, Valsartan 138402-11-6, Irbesartan 143003-46-7, Alglucerase 144494-65-5, Tirofiban 144701-48-4, Telmisartan 145599-86-6, Cerivastatin 147059-72-1, Trovafloxacin 147245-92-9, Copolymer 1 150378-17-9, Indinavir 151096-09-2, Moxifloxacin 161814-49-9, Amprenavir 169590-42-5, Celecoxib 171599-83-0, Sildenafil citrate 172820-23-4, Pexiganan acetate 180288-69-1, Trastuzumab 185243-69-0, Etanercept 188627-80-7, Eptifibatide 339524-26-4, Amiodorone 339524-30-0, Cyclopegic 339524-35-5, Cytoxin 339524-50-4, Hyperozia
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT **97322-87-7**, Troglitazone **111025-46-8**, Pioglitazone **122320-73-4**, Rosiglitazone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

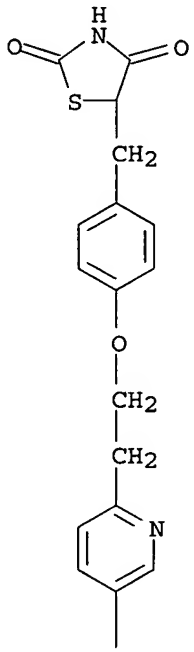
study, unclassified); BIOL (Biological study)
(methods of determining individual hypersensitivity to a pharmaceutical agent
from gene expression profile)

RN 97322-87-7 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 111025-46-8 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

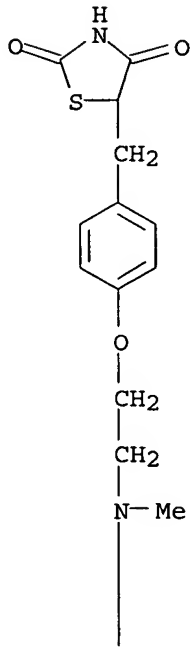


PAGE 2-A

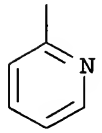
RN 122320-73-4 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



L148 ANSWER 16 OF 56 MEDLINE on STN DUPLICATE 1

ACCESSION NUMBER: 2004273852 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15174093
TITLE: Decreased expression of peroxisome proliferator activated receptor gamma in **cftr**-/- mice.
AUTHOR: Ollero Mario; Junaidi Omer; Zaman Munir M; Tzameli Iphigenia; Ferrando Adolfo A; Andersson Charlotte; Blanco Paola G; Bialecki Eldad; Freedman Steven D
CORPORATE SOURCE: Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA.
CONTRACT NUMBER: R01 DK52765 (NIDDK)
SOURCE: Journal of cellular physiology, (2004 Aug) 200 (2) 235-44. Journal code: 0050222. ISSN: 0021-9541.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200408
ENTRY DATE: Entered STN: 20040603
Last Updated on STN: 20040817
Entered Medline: 20040816

ABSTRACT:
Some of the pathological manifestations of **cystic fibrosis** are in accordance with an impaired expression and/or activity of PPARgamma. We hypothesized that PPARgamma expression is altered in tissues lacking the normal ***cystic*** **fibrosis** transmembrane regulator protein (**CFTR**). PPARgamma mRNA levels were measured in colonic mucosa, ileal mucosa, adipose tissue, lung, and liver from wild-type and **cftr**-/- mice by quantitative RT-PCR. PPARgamma expression was decreased twofold in ***CFTR*** -regulated tissues (colon, ileum, and lung) from **cftr**-/- mice compared to wild-type littermates. In contrast, no differences were found in fat and liver. Immunohistochemical analysis of PPARgamma in ileum and colon revealed a predominantly nuclear localization in wild-type mucosal epithelial cells while tissues from **cftr**-/- mice showed a more diffuse, lower intensity labeling. A significant decrease in PPARgamma expression was confirmed in nuclear extracts of colon mucosa by Western blot analysis. In addition, binding of the PPARgamma/RXR heterodimer to an oligonucletotide containing a peroxisome proliferator responsive element (PPRE) was also decreased in colonic mucosa extracts from **cftr**-/- mice. Treatment of ***cftr*** -/- mice with the PPARgamma ligand **rosiglitazone** restored both the nuclear localization and binding to DNA, but did not increase RNA levels. We conclude that PPARgamma expression in **cftr**-/- mice is downregulated at the RNA and protein levels and its function diminished. These changes may be related to the loss of function of **CFTR** and may be relevant to the pathogenesis of metabolic abnormalities associated with ***cystic*** **fibrosis** in humans.

CONTROLLED TERM: Check Tags: Comparative Study
Animals
Blotting, Western
Cystic Fibrosis Transmembrane Conductance Regulator: DF, deficiency
Cystic Fibrosis Transmembrane Conductance Regulator: GE, genetics
***Cystic Fibrosis Transmembrane Conductance Regulator: ME, metabolism**
Down-Regulation
Fibrinolytic Agents: PD, pharmacology
Gene Expression Regulation
Immunohistochemistry
Intestinal Mucosa: DE, drug effects
Intestinal Mucosa: ME, metabolism
Mice
Mice, Knockout
RNA, Messenger: ME, metabolism
Receptors, Cytoplasmic and Nuclear: GE, genetics
*Receptors, Cytoplasmic and Nuclear: ME, metabolism
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Reverse Transcriptase Polymerase Chain Reaction
Thiazolidinediones: PD, pharmacology
Transcription Factors: GE, genetics
*Transcription Factors: ME, metabolism

CAS REGISTRY NO.: **122320-73-4 (rosiglitazone); 126880-72-6**

(**Cystic Fibrosis Transmembrane Conductance Regulator**)
CHEMICAL NAME: 0 (Fibrinolytic Agents); 0 (RNA, Messenger); 0 (Receptors, Cytoplasmic and Nuclear); 0 (**Thiazolidinediones**); 0 (Transcription Factors)

L148 ANSWER 17 OF 56 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2003409634 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12946210
TITLE: Genomics, transcriptomics, proteomics, and numbers.
AUTHOR: Kiechle Frederick L; Holland-Staley Carol A
CORPORATE SOURCE: Department of Clinical Pathology, William Beaumont Hospital, Royal Oak, Mich 48073, USA.. fkiechle@beaumont.edu
SOURCE: Archives of pathology & laboratory medicine, (2003 Sep) 127 (9) 1089-97. Ref: 126
Journal code: 7607091. ISSN: 1543-2165.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030903
Last Updated on STN: 20031021
Entered Medline: 20031020

ABSTRACT:
OBJECTIVE: To review the advances in clinically useful molecular biologic techniques and to identify their applications in clinical practice, as presented at the 11th Annual William Beaumont Hospital DNA Symposium. DATA SOURCES: The 8 manuscripts submitted were reviewed, and their major findings were compared with literature on the same or related topics. STUDY SELECTION: Manuscripts address the use of molecular techniques in microbiology to evaluate infectious disease and epidemiology; molecular microbiology methods, including rapid-cycle real-time polymerase chain reaction; peroxisome proliferator-activated receptor gamma as a potential therapeutic target in inflammatory bowel disease or colon cancer; the effect of nonapoptotic doses of the bisbenizamide dye Hoechst 33342 on luciferase expression in plasmid-transfected BC3H-1 myocytes; the routine use of **cystic** ***fibrosis*** screening and its challenges; and the use of flow cytometry and/or chromosomal translocation in the diagnostic evaluation of hematopoietic malignancies. DATA SYNTHESIS: Three current issues related to the use of molecular tests in clinical laboratories are (1) the restriction on introducing new tests secondary to existing patents or licenses; (2) the preanalytic variables for the different specimen types currently in use, including whole blood, plasma, serum, fresh or frozen tissues, and free-circulating DNA; and (3) the interpretation of studies evaluating the association of complex diseases with a single mutation or single-nucleotide polymorphism. Molecular methods have had a major impact on infectious disease through the rapid identification of organisms, the evaluation of outbreaks, and the characterization of drug resistance when compared with standard culture techniques. The activation of peroxisome proliferator-activated receptor gamma stimulated by **thiazolidinedione** is useful in the treatment of type II diabetes mellitus and may have value in preventing inflammatory bowel disease or colon cancer. Hoechst 33342 binding to adenine-thymine-rich regions in the minor groove of DNA is a fluorescent stain for DNA and initiates apoptosis at >10 microg/mL. Lower doses of Hoechst 33342 promote luciferase expression by a mechanism that may involve binding to cryptic promoters facilitated by dye-associated misalignment of the tertiary structure of DNA. The routine use of **cystic fibrosis** screening is complicated by the more

than 1000 mutations associated with the disease. The use of 4-color flow cytometry and the detection of chromosomal translocation are both invaluable aids in establishing the diagnosis of lymphoid or myeloid hematopoietic malignancies. CONCLUSIONS: The current postgenomic era will continue to emphasize the use of microarrays and database software for genomic, transcriptomic, and proteomic screening in the search for useful clinical assays. The number of molecular pathologic techniques will expand as additional disease-associated mutations are defined.

CONTROLLED TERM: **Cystic Fibrosis: DI, diagnosis**
Cystic Fibrosis: GE, genetics
Genetic Screening: MT, methods
*Genomics: MT, methods
Genomics: TD, trends
Humans
Pathology, Clinical: MT, methods
Pathology, Clinical: TD, trends
Polymerase Chain Reaction: MT, methods
Polymorphism, Single Nucleotide
*Proteomics: MT, methods
Proteomics: TD, trends
*Transcription, Genetic: GE, genetics

L148 ANSWER 18 OF 56 MEDLINE on STN
ACCESSION NUMBER: 2005488677 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15905414
TITLE: A novel small molecule **CFTR** inhibitor attenuates HCO3- secretion and duodenal ulcer formation in rats.
AUTHOR: Akiba Yasutada; Jung Michael; Ouk Samedy; Kaunitz Jonathan D
CORPORATE SOURCE: Department of Medicine, University of California, Los Angeles, USA.
CONTRACT NUMBER: P30-DK-0413 (NIDDK)
R01-DK-54221 (NIDDK)
SOURCE: American journal of physiology. Gastrointestinal and liver physiology, (2005 Oct) 289 (4) G753-9. Electronic Publication: 2005-05-19.
Journal code: 100901227. ISSN: 0193-1857.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200510
ENTRY DATE: Entered STN: 20050915
Last Updated on STN: 20051028
Entered Medline: 20051027

ABSTRACT:
The **cystic fibrosis** (CF) transmembrane conductance regulator (**CFTR**) plays a crucial role in mediating duodenal bicarbonate (HCO(3)(-)) secretion (DBS). Although impaired DBS is observed in CF mutant mice and in CF patients, which would predict increased ulcer susceptibility, duodenal injury is rarely observed in CF patients and is reduced in CF mutant mice. To explain this apparent paradox, we hypothesized that **CFTR** dysfunction increases cellular [HCO(3)(-)] and buffering power. To further test this hypothesis, we examined the effect of a novel, potent, and highly selective **CFTR** inhibitor, **CFTR**(inh)-172, on DBS and duodenal ulceration in rats. DBS was measured in situ using a standard loop perfusion model with a pH stat under isoflurane anesthesia. Duodenal ulcers were induced in rats by cysteamine with or without **CFTR** (inh)-172 pretreatment 1 h before cysteamine. Superfusion of **CFTR** (inh)-172 (0.1-10 microM) over the duodenal mucosa had no effect on basal DBS

but at 10 microM inhibited acid-induced DBS, suggesting that its effect was limited to **CFTR** activation. Acid-induced DBS was abolished at 1 and 3 h and was reduced 24 h after treatment with **CFTR**(inh)-172, although basal DBS was increased at 24 h. **CFTR**(inh)-172 treatment had no effect on gastric acid or HCO(3)(-) secretion. Duodenal ulcers were observed 24 h after cysteamine treatment but were reduced in **CFTR**(inh)-172-pretreated rats. **CFTR**(inh)-172 acutely produces ***CFTR*** dysfunction in rodents for up to 24 h. **CFTR** inhibition reduces acid-induced DBS but also prevents duodenal ulcer formation, supporting our hypothesis that intracellular HCO(3)(-) may be an important protective mechanism for duodenal epithelial cells.

CONTROLLED TERM: Check Tags: Male
Animals
*Benzoic Acids: PD, pharmacology
*Bicarbonates: ME, metabolism
Chromatography, High Pressure Liquid
Cystamine: TO, toxicity
***Cystic Fibrosis Transmembrane Conductance Regulator: AI, antagonists & inhibitors**
Cystic Fibrosis Transmembrane Conductance Regulator: ME, metabolism
Duodenal Ulcer: CI, chemically induced
*Duodenal Ulcer: PC, prevention & control
Duodenum: DE, drug effects
Duodenum: ME, metabolism
Gastric Acid: SE, secretion
Rats
Rats, Sprague-Dawley
Research Support, N.I.H., Extramural
Research Support, U.S. Gov't, Non-P.H.S.
Research Support, U.S. Gov't, P.H.S.
Sulfhydryl Reagents: TO, toxicity
*Thiazoles: PD, pharmacology

CAS REGISTRY NO.: **126880-72-6 (Cystic Fibrosis Transmembrane Conductance Regulator)**; 51-85-4 (Cystamine)

CHEMICAL NAME: 0 (3-((3-trifluoromethyl)phenyl)-5-((3-carboxyphenyl)methylene)-**2-thioxo-4-thiazolidinone**); 0 (Benzoic Acids); 0 (Bicarbonates); 0 (Sulfhydryl Reagents); 0 (Thiazoles)

L148 ANSWER 19 OF 56 MEDLINE on STN
ACCESSION NUMBER: 2005551230 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16081479
TITLE: Disruption of **CFTR** chloride channel alters mechanical properties and cAMP-dependent Cl- transport of mouse aortic smooth muscle cells.
AUTHOR: Robert Renaud; Norez Caroline; Becq Frederic
CORPORATE SOURCE: Institut de Physiologie et Biologie Cellulaires, CNRS UMR 6187, Universite de Poitiers, France.
SOURCE: The Journal of physiology, (2005 Oct 15) 568 (Pt 2) 483-95. Electronic Publication: 2005-08-04.
Journal code: 0266262. ISSN: 0022-3751.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200512
ENTRY DATE: Entered STN: 20051018
Last Updated on STN: 20051228
Entered Medline: 20051227

ABSTRACT:
Chloride (Cl(-)) channels expressed in vascular smooth muscle cells (VSMC) are important to control membrane potential equilibrium, intracellular pH, cell volume maintenance, contraction, relaxation and proliferation. The present study was designed to compare the expression, regulation and function of ***CFTR*** Cl(-) channels in aortic VSMC from **Cftr**(+/+) and ***Cftr*** (-)(/)(-) mice. Using an iodide efflux assay we demonstrated stimulation of **CFTR** by VIP, isoproterenol, cAMP agonists and other pharmacological activators in cultured VSMC from **Cftr**(+/+). On the contrary, in cultured VSMC from **Cftr**(-)(/)(-) mice these agonists have no effect, showing that **CFTR** is the dominant Cl(-) channel involved in the response to cAMP mediators. Angiotensin II and the calcium ionophore A23187 stimulated Ca(2)(+)-dependent Cl(-) channels in VSMCs from both genotypes. **CFTR** was activated in myocytes maintained in medium containing either high potassium or 5-hydroxytryptamine (5-HT) and was inhibited by **CFTR**(inh)-172, glibenclamide and diphenylamine-2,2'-dicarboxylic acid (DPC). We also examined the mechanical properties of aortas. Arteries with or without endothelium from **Cftr**(-/-) mice became significantly more constricted (approximately 2-fold) than that of **Cftr** (+/+) mice in response to vasoactive agents. Moreover, in precontracted arteries of **Cftr**(+/+) mice, VIP and **CFTR** activators induced vasorelaxation that was altered in **Cftr**(-/-) mice. Our findings suggest a novel mechanism for regulation of the vascular tone by cAMP-dependent ***CFTR*** chloride channels in VSMC. To our knowledge this study is the first to report the phenotypic consequences of the loss of a Cl(-) channel on vascular reactivity.

CONTROLLED TERM:
Adrenergic beta-Agonists: PD, pharmacology
Angiotensin II: PD, pharmacology
Animals
Anthranilic Acids: PD, pharmacology
Aorta, Thoracic
Benzoic Acids: PD, pharmacology
Cells, Cultured
Chlorides: ME, metabolism
Cystic Fibrosis Transmembrane Conductance Regulator: DF, deficiency
Cystic Fibrosis Transmembrane Conductance Regulator: DE, drug effects
***Cystic Fibrosis Transmembrane Conductance Regulator: PH, physiology**
Forskolin: PD, pharmacology
Genistein: PD, pharmacology
Glyburide: PD, pharmacology
In Vitro
Isoproterenol: PD, pharmacology
Mice
Mice, Inbred CFTR
Muscle, Smooth, Vascular: DE, drug effects
Muscle, Smooth, Vascular: EN, enzymology
*Muscle, Smooth, Vascular: ME, metabolism
Quinolizines: PD, pharmacology
Research Support, Non-U.S. Gov't
Serotonin: PD, pharmacology
Thiazoles: PD, pharmacology
Vasoactive Intestinal Peptide: PD, pharmacology
Vasoconstriction
Vasoconstrictor Agents: PD, pharmacology
Vasodilation
Vasodilator Agents: PD, pharmacology

CAS REGISTRY NO.: 10238-21-8 (Glyburide); 11128-99-7 (Angiotensin II);

126880-72-6 (Cystic Fibrosis Transmembrane Conductance Regulator); 37221-79-7 (Vasoactive Intestinal Peptide); 446-72-0 (Genistein); 50-67-9 (Serotonin); 66428-89-5 (Forskolin); 7683-59-2 (Isoproterenol); 91-40-7 (fenamic acid)

CHEMICAL NAME: 0 (3-((3-trifluoromethyl)phenyl)-5-((3-carboxyphenyl)methylene)-**2-thioxo-4-thiazolidinone**); 0 (6-hydroxy-10-chlorobenzo(c)quinolizinium); 0 (Adrenergic beta-Agonists); 0 (Anthranilic Acids); 0 (Benzoic Acids); 0 (Chlorides); 0 (Quinolizines); 0 (Thiazoles); 0 (Vasoconstrictor Agents); 0 (Vasodilator Agents)

L148 ANSWER 20 OF 56 MEDLINE on STN
ACCESSION NUMBER: 2004299977 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15201289
TITLE: Dopaminergic and serotonergic innervation of cockroach salivary glands: distribution and morphology of synapses and release sites.
AUTHOR: Baumann Otto; Kuhnel Dana; Dames Petra; Walz Bernd
CORPORATE SOURCE: Institut fur Biochemie und Biologie, Zoophysiologie, Universitat Potsdam, Postfach 601553, D-14415 Potsdam, Germany.. obaumann@rz.uni.potsdam.de
SOURCE: Journal of experimental biology, (2004 Jul) 207 (Pt 15) 2565-75.
Journal code: 0243705. ISSN: 0022-0949.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200502
ENTRY DATE: Entered STN: 20040618
Last Updated on STN: 20050301
Entered Medline: 20050224

ABSTRACT:
The paired salivary glands in the cockroach are composed of acini with ***ion*** -**transporting** peripheral P-cells and protein-secreting central C-cells, and a duct system for the modification of the primary saliva. Secretory activity is controlled by serotonergic and dopaminergic neurons, whose axons form a dense plexus on the glands. The spatial relationship of release sites for serotonin and dopamine to the various cell types was determined by anti-synapsin immunofluorescence confocal microscopy and electron microscopy. Every C-cell apparently has only serotonergic synapses on its surface. Serotonergic and dopaminergic fibres on the acini have their release zones at a distance of approximately 0.5 microm from the P-cells. Nerves between acinar lobules may serve as neurohaemal organs and contain abundant dopaminergic and few serotonergic release sites. Some dopaminergic and serotonergic release sites reside in the duct epithelium, the former throughout the duct system, the latter only in segments next to acini. These findings are consistent with the view that C-cells respond exclusively to serotonin, P-cells to serotonin and dopamine, and most duct cells only to dopamine. Moreover, the data suggest that C-cells are stimulated by serotonin released close to their surface, whereas P-cells and most duct cells are exposed to serotonin/dopamine liberated at some distance.

CONTROLLED TERM: Check Tags: Comparative Study
Animals
Blotting, Western
*Cockroaches: ME, metabolism
Dopamine: SE, secretion
Microscopy, Electron

Microscopy, Fluorescence
*Neurosecretory Systems: CY, cytology
Salivary Glands: CY, cytology
*Salivary Glands: IR, innervation
Serotonin: SE, secretion
Synapses: SE, secretion
*Synapses: UL, ultrastructure
Synapsins
Thiazolidinediones

CAS REGISTRY NO.: 50-67-9 (Serotonin); 51-61-6 (Dopamine); **79714-31-1 (CT 112)**
CHEMICAL NAME: 0 (Synapsins); 0 (Thiazolidinediones)

L148 ANSWER 21 OF 56 MEDLINE on STN
ACCESSION NUMBER: 2004525858 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15496164
TITLE: The relationship between cell proliferation, Cl- secretion, and renal cyst growth: a study using **CFTR** inhibitors.
AUTHOR: Li Hongyu; Findlay Iain A; Sheppard David N
CORPORATE SOURCE: Department of Physiology, University of Bristol, School of Medical Sciences, University Walk, Bristol, United Kingdom.
SOURCE: Kidney international, (2004 Nov) 66 (5) 1926-38.
Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200504
ENTRY DATE: Entered STN: 20041022
Last Updated on STN: 20050426
Entered Medline: 20050425

ABSTRACT:
BACKGROUND: In autosomal-dominant polycystic kidney disease (ADPKD), cAMP-stimulated cell proliferation and Cl- secretion via the **cystic** ***fibrosis*** transmembrane conductance regulator (**CFTR**) Cl- channel drive the enlargement of fluid-filled epithelial cysts. To investigate how **CFTR** blockers inhibit cyst growth, we studied cAMP-dependent Cl- secretion, cell proliferation, and cyst growth using type I Madin Darby canine kidney (MDCK) cells as a model of renal cyst development and growth. METHODS: We grew MDCK cysts in collagen gels in the presence of the cAMP agonist forskolin, measured Cl- secretion with the Ussing chamber technique, and assayed cell proliferation using nonpolarized and polarized MDCK cells. To inhibit **CFTR**, we used glibenclamide, 5-nitro-2-(3-phenylpropylamino)-benzoic acid (NPPB), genistein, and the specific **CFTR** inhibitor ***CFTRinh*** -172. As controls, we tested the effects of blockers of other types of apical membrane Cl- channels and inhibitors of basolateral membrane ion channels and transporters. RESULTS: In the absence of inhibitors of transepithelial ion transport, forskolin stimulated dramatic cyst growth. ***CFTR*** blockers and inhibitors of basolateral membrane ion channels and transporters retarded cyst growth. In contrast, blockers of other types of apical membrane Cl- channels, which were without effect on **CFTR**, failed to inhibit cyst growth. Inhibition of cyst growth by **CFTR** blockers was correlated with inhibition of cAMP-stimulated Cl- current (correlation coefficient = 0.81; $P < 0.05$), but not cell proliferation (correlation coefficient = 0.50; $P > 0.05$). CONCLUSION: Our data suggest that ***CFTR*** blockers might retard cyst growth predominantly by inhibiting fluid accumulation within the cyst lumen.
CONTROLLED TERM: Animals
Benzoic Acids: PD, pharmacology

Cell Division: DE, drug effects
Cell Line
Chloride Channels: ME, metabolism
*Chlorides: ME, metabolism
Cyclic AMP: PD, pharmacology
Cystic Fibrosis Transmembrane Conductance Regulator: AI, antagonists & inhibitors
Dogs
Electric Conductivity
Epithelium: ME, metabolism
Forskolin: PD, pharmacology
Genistein: PD, pharmacology
Glyburide: PD, pharmacology
Ion Transport: DE, drug effects
*Kidney, Cystic: ME, metabolism
*Kidney, Cystic: PA, pathology
Kidney, Cystic: PC, prevention & control
Nitrobenzoates: PD, pharmacology
Research Support, Non-U.S. Gov't
Thiazoles: PD, pharmacology

CAS REGISTRY NO.: 10238-21-8 (Glyburide); 107254-86-4 (5-nitro-2-(3-phenylpropylamino)benzoic acid); **126880-72-6 (Cystic Fibrosis Transmembrane Conductance Regulator)**; 446-72-0 (Genistein); 60-92-4 (Cyclic AMP); 66428-89-5 (Forskolin)

CHEMICAL NAME: 0 (3-((3-trifluoromethyl)phenyl)-5-((3-carboxyphenyl)methylene)-**2-thioxo-4-thiazolidinone**); 0 (Benzoic Acids); 0 (Chloride Channels); 0 (Chlorides); 0 (Nitrobenzoates); 0 (Thiazoles)

L148 ANSWER 22 OF 56 MEDLINE on STN
ACCESSION NUMBER: 2004336281 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15131065
TITLE: Effects of a new **cystic fibrosis** transmembrane conductance regulator inhibitor on Cl- conductance in human sweat ducts.
AUTHOR: Wang X F; Reddy M M; Quinton P M
CORPORATE SOURCE: Department of Pediatrics, UCSD, 9500 Gilman Drive, La Jolla, CA 92093-0831, USA.. pquinton@ucsd.edu
CONTRACT NUMBER: DE14352 (NIDCR)
DK51899 (NIDDK)
SOURCE: Experimental physiology, (2004 Jul) 89 (4) 417-25. Electronic Publication: 2004-05-06.
Journal code: 9002940. ISSN: 0958-0670.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200410
ENTRY DATE: Entered STN: 20040708
Last Updated on STN: 20041019
Entered Medline: 20041018

ABSTRACT:
Effective and specific inhibition of the **cystic fibrosis** transmembrane conductance regulator (**CFTR**) Cl- channel in epithelia has long been needed to better understand the role of anion movements in fluid and electrolyte transport. Until now, available inhibitors have required high concentrations, usually in the millimolar or high micromolar range, to effect even an incomplete block of channel conductance. These inhibitors, including

5-nitro-2(3-phenylpropyl-amino)benzoate (NPPB), bumetamide, glibenclamide and DIDS, are also relatively non-specific. Recently a new anion channel inhibitor, a thiazolidinone derivative, termed **CFTRInh**-172 has been synthesized and introduced with apparently improved inhibitory properties as shown by effects on anion conductance expressed in cell lines and on secretion in vivo. Here, we assay the effect of this inhibitor on a purely salt absorbing native epithelial tissue, the freshly isolated microperfused human sweat duct, known for its inherently high expression of **CFTR**. We found that the inhibitor at a maximum dose limited by its aqueous solubility of 5 microm partially blocked **CFTR** when applied to either surface of the membrane; however, it may be somewhat more effective from the cytosolic side (approximately 70% inhibition). It may also partially inhibit Na+ conductance. The inhibition was relatively slow, with a half time for maximum effect of about 3 min, and showed very slow reversibility. Results also suggest that ***CFTR*** Cl- conductance (GCl) was blocked in both apical and basal membranes. The inhibitor appears to exert some effect on Na+ transport as well.

CONTROLLED TERM: Check Tags: In Vitro
*Benzoic Acids: PD, pharmacology
*Chlorides: ME, metabolism
***Cystic Fibrosis Transmembrane Conductance Regulator: AI, antagonists & inhibitors**
***Cystic Fibrosis Transmembrane Conductance Regulator: ME, metabolism**
Cytosol: ME, metabolism
Humans
Phosphorylation
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Sodium Chloride: ME, metabolism
Sweat Glands: DE, drug effects
*Sweat Glands: ME, metabolism
*Thiazoles: PD, pharmacology

CAS REGISTRY NO.: **126880-72-6 (Cystic Fibrosis Transmembrane Conductance Regulator)**; 7647-14-5 (Sodium Chloride)

CHEMICAL NAME: 0 (3-((3-trifluoromethyl)phenyl)-5-((3-carboxyphenyl)methylene)-**2-thioxo-4-thiazolidinone**); 0 (Benzoic Acids); 0 (Chlorides); 0 (Thiazoles)

L148 ANSWER 23 OF 56 MEDLINE on STN
ACCESSION NUMBER: 2003506810 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14583425
TITLE: Thiazolidinediones, peripheral edema, and type 2 diabetes: incidence, pathophysiology, and clinical implications.
AUTHOR: Mudaliar Sunder; Chang Anna R; Henry Robert R
CORPORATE SOURCE: Section of Diabetes and Metabolism, VA San Diego HealthCare System, California 92161, USA.
SOURCE: Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists, (2003 Sep-Oct) 9 (5) 406-16.
Ref: 40
Journal code: 9607439. ISSN: 1530-891X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404

ENTRY DATE: Entered STN: 20031030
Last Updated on STN: 20040407
Entered Medline: 20040406

ABSTRACT:
OBJECTIVE: To present an objective, evidence-based review of edema associated with thiazolidinedione use in patients with type 2 diabetes. METHODS: We review the incidence, pathophysiology, and clinical significance of edema associated with the use of thiazolidinediones, with specific emphasis on the two currently available thiazolidinediones, rosiglitazone and pioglitazone. RESULTS: Both pioglitazone and rosiglitazone have been associated with increased development of edema in clinical trials. The incidence of edema in these trials varies from about 3.0 to 7.5% with the thiazolidinediones compared with 1.0 to 2.5% with placebo or other oral antidiabetic therapy. The highest incidence of edema has been reported when thiazolidinediones are used in combination with insulin. In clinical studies, these patients have an incidence of edema of 15.3% when treated with insulin plus pioglitazone and 14.7% when treated with insulin plus rosiglitazone (compared with 7.0% and 5.4% in the insulin-only groups, respectively). In addition to peripheral edema, reports have described pulmonary edema associated with thiazolidinedione therapy. In all such reports, patients failed to respond to diuretics during use of thiazolidinediones. Clinical improvement ensued only after discontinuation of thiazolidinedione therapy. Therefore, thiazolidinediones either may have some effect on the delivery of diuretics to the lumen of the nephron or may induce tubular alterations that impair the ability of the nephrons to respond to diuretics. Several potential causes have been postulated to precipitate edema in patients with diabetes who are treated with these agents: increased plasma volume, increased renal sodium reabsorption, reflex sympathetic activation, alteration of intestinal **ion** ***transport*** , and increased production of vascular endothelial growth factor. CONCLUSION: Available evidence suggests that edema is a class effect of the thiazolidinediones and is multifactorial in origin. Thiazolidinedione-associated edema seems to be dose related and occurs most frequently when thiazolidinediones are used in combination with insulin. Hence, therapy with these agents should be initiated at low doses, and patients should undergo assessment for edema and congestive heart failure during the first few weeks of treatment. Caution should be exercised when thiazolidine-diones are used in those at risk for or with a history of heart failure. Options for management thiazolidinedione-associated edema include dose reduction, drug discontinuation, and symptomatic therapy with diuretics. Further studies are needed to elucidate the mechanisms responsible for the cause of edema in patients with type 2 diabetes treated with thiazolidinediones and to determine whether certain factors might predict susceptibility to development of edema and congestive heart failure.

CONTROLLED TERM: *Diabetes Mellitus, Type 2: DT, drug therapy
Diabetes Mellitus, Type 2: EP, epidemiology
Diabetes Mellitus, Type 2: PP, physiopathology
*Edema: CI, chemically induced
Edema: EP, epidemiology
Edema: PP, physiopathology
Humans
*Hypoglycemic Agents: AE, adverse effects
*Thiazolidinediones: AE, adverse effects

CAS REGISTRY NO.: **2295-31-0 (2,4-thiazolidinedione)**

CHEMICAL NAME: 0 (Hypoglycemic Agents); 0 (Thiazolidinediones)

L148 ANSWER 24 OF 56 MEDLINE on STN

ACCESSION NUMBER: 2003503750 MEDLINE

DOCUMENT NUMBER: PubMed ID: 14581143

TITLE: Effects of an aldose reductase inhibitor on gastroenteropathy in streptozotocin-diabetic rats.

AUTHOR: Oya M; Hosokawa M; Tsukada H; Fukuda K; Nakamura H; Tsukiyama K; Nagashima K; Fujimoto S; Yamada Y; Seino Y
CORPORATE SOURCE: Department of Diabetes and Clinical Nutrition, Graduate School of Medicine, Kyoto University, 54, Shogoin, Kawara-machi, Sakyo-ku, Kyoto 606-8507, Japan.
SOURCE: Diabetes research and clinical practice, (2003 Nov) 62 (2) 69-77.
Journal code: 8508335. ISSN: 0168-8227.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200407
ENTRY DATE: Entered STN: 20031029
Last Updated on STN: 20040713
Entered Medline: 20040712

ABSTRACT:
We investigated the effects of epalrestat, an aldose reductase inhibitor (ARI), on gastric emptying, fecal water content, and electrolyte transport in distal colon in streptozotocin (STZ)-induced diabetic rats. We measured gastric emptying time by acetaminophen method and short-circuit-current (Isc) in colonic mucosa using an Ussing chamber. The Isc in response to electric-field-stimulation (EFS) was decreased in untreated rats due to suppression by Cl- secretion. ARI treatment alleviated this suppression (2.7 +/- 0.6 vs. 7.4 +/- 1.1 microA/0.38 cm2 at 8 weeks after treatment, 1.1 +/- 0.2 vs. 7.0 +/- 1.0 at 12 weeks after treatment, P<0.05). In addition, the percentage of fecal water content in untreated rats was significantly lower than in ARI-treated rats (58.0 +/- 2.0 vs. 67.6 +/- 0.8% at 8 weeks, 56.9 +/- 2.1 vs. 63.4 +/- 1.4 at 12 weeks, P<0.05). From STZ injection to 8 weeks, the serum levels of acetaminophen in the diabetic rats were significantly lower than in controls, indicating delayed gastric emptying. At 12 weeks in the diabetic rats treated with ARI, the serum levels of acetaminophen were significantly higher than in the untreated diabetic rats (6.6 +/- 0.4 vs. 3.5 +/- 0.5 microg/ml, P<0.05). ARI-treatment ameliorated delayed gastric emptying without improving glycemic control. These findings show that ARI partially prevented progression of impaired gastric emptying, **ion ***transport*** , and water **transport**, and suggest that epalrestat might be useful in the treatment of diabetic gastroenteropathy.

CONTROLLED TERM: Check Tags: Male
Acetaminophen: PK, pharmacokinetics
*Aldehyde Reductase: AI, antagonists & inhibitors
Animals
Blood Glucose: DE, drug effects
Blood Glucose: ME, metabolism
Body Water: ME, metabolism
Colon: DE, drug effects
*Colon: PP, physiopathology
*Diabetes Mellitus, Experimental: CO, complications
*Diabetes Mellitus, Experimental: PP, physiopathology
Electrolytes: ME, metabolism
*Enzyme Inhibitors: PD, pharmacology
Feces
Gastric Emptying: DE, drug effects
Intestinal Mucosa: DE, drug effects
*Intestinal Mucosa: PP, physiopathology
Rats
Rats, Wistar
Research Support, Non-U.S. Gov't
*Rhodanine: AA, analogs & derivatives
*Rhodanine: PD, pharmacology

Tetrodotoxin: PD, pharmacology
Time Factors
CAS REGISTRY NO.: 103-90-2 (Acetaminophen); **141-84-4 (Rhodanine)**; 4368-28-9 (Tetrodotoxin); **82159-09-9 (ONO 2235)**
CHEMICAL NAME: 0 (Blood Glucose); 0 (Electrolytes); 0 (Enzyme Inhibitors); EC 1.1.1.21 (Aldehyde Reductase)

L148 ANSWER 25 OF 56 MEDLINE on STN
ACCESSION NUMBER: 2001460379 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11340303
TITLE: Troglitazone stimulates basolateral rheogenic Na+/HCO3- cotransport activity in rabbit proximal straight tubules.
AUTHOR: Muto S; Miyata Y; Imai M; Asano Y
CORPORATE SOURCE: Department of Nephrology, Jichi Medical School, Kawachi, Tochigi, Japan.. smuto@jichi.ac.jp
SOURCE: Experimental nephrology, (2001) 9 (3) 191-7.
Journal code: 9302239. ISSN: 1018-7782.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010820
Last Updated on STN: 20010820
Entered Medline: 20010816

ABSTRACT:
Thiazolidinedione derivatives, new insulin-sensitizing antidiabetic agents, are expected to have potential clinical use. Since these drugs cause edema in a variable proportion of patients, we examined whether troglitazone (Tro) has direct action on Na+ transport of rabbit proximal straight tubule perfused in vitro. For this purpose, we measured basolateral membrane voltage (V(B)) by conventional microelectrode techniques and intracellular pH (pH(i)) by microscopic fluorescence spectrophotometry with a pH-sensitive fluorescent dye, 2', 7'-bis-2-carboxyethyl-5-carboxyfluorescein. Tro at 50 microM in the bath significantly depolarized both transepithelial voltage and V(B). To examine whether the basolateral rheogenic Na+/HCO3- cotransport activity is affected by Tro, we observed V(B) deflection upon abrupt 10-fold decrease in bath HCO3- in the absence and presence of Tro. The apparent transference number of HCO3- (tHCO3), as calculated from the V(B) deflection, was significantly greater in the presence of Tro (50 microM) than that seen in its absence. Tro caused cell acidification and increased the intracellular acidification rates (dpH(i)/dt) upon abrupt 10-fold decreases in bath HCO3- and Na+ concentrations. The stimulatory effects of Tro on tHCO3 and dpH(i)/dt were dose dependent between 5 and 50 miccroM, but they were unaffected at 0.5 microM. From these results, we conclude that Tro acts on the proximal straight tubule and stimulates the basolateral rheogenic Na+/HCO3- cotransport activity. The stimulatory action of Tro may partly account for edema formation.

CONTROLLED TERM: Check Tags: In Vitro; Male
*Acidosis: ME, metabolism
Animals
*Bicarbonates: ME, metabolism
*Cell Membrane: DE, drug effects
Cell Membrane: PH, physiology
*Cell Polarity: DE, drug effects
*Chromans: PK, pharmacokinetics
*Chromans: PD, pharmacology
Dose-Response Relationship, Drug
Electrophysiology
Hydrogen-Ion Concentration

***Ion Transport: DE, drug effects**
*Kidney Tubules, Proximal: DE, drug effects
*Kidney Tubules, Proximal: PH, physiology
*Membrane Potentials: DE, drug effects
Perfusion
Rabbits
Research Support, Non-U.S. Gov't
Sodium: BL, blood
*Sodium: ME, metabolism
*Sodium-Hydrogen Antiporter: ME, metabolism
Spectrometry, Fluorescence
*Thiazoles: PK, pharmacokinetics
*Thiazoles: PD, pharmacology
*Thiazolidinediones
CAS REGISTRY NO.: 7440-23-5 (Sodium); **97322-87-7 (troglitazone)**
CHEMICAL NAME: 0 (Bicarbonates); 0 (Chromans); 0 (Sodium-Hydrogen Antiporter); 0 (Thiazoles); 0 (Thiazolidinediones)

L148 ANSWER 26 OF 56 MEDLINE on STN
ACCESSION NUMBER: 2000155279 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10693612
TITLE: Marathon with **cystic fibrosis** and bilateral lung transplant.
AUTHOR: Stanghelle J K; Koss J O; Bjortuft O; Geiran O
CORPORATE SOURCE: Sunnaas Rehabilitation Hospital, Nesoddtangen, Norway.
SOURCE: Scandinavian journal of medicine & science in sports, (2000 Feb) 10 (1) 42-6.
Journal code: 9111504. ISSN: 0905-7188.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000327
Last Updated on STN: 20000327
Entered Medline: 20000315

ABSTRACT:
The article presents studies performed before, during and after a marathon run (42,195 m) in a 32-year-old man who underwent a bilateral lung transplantation because of end-stage **cystic fibrosis** (CF) 15 months prior to the race. Before the run his FEV1 was 81% predicted, compared with 19% predicted before the operation, and his maximal oxygen uptake was 31.9 ml/kg(-1)/min(-1). He completed the New York City Marathon 1998 without major problems in 7 **h** 8 min 50s. Pulmonary tests, biochemical changes and endocrine responses indicated transient changes, mostly as expected in healthy marathon runners. The case demonstrates that physiological trainability and psychological will power following a successful bilateral lung transplantation can transform a chronically ill CF patient into a robust marathon runner.

CONTROLLED TERM: Check Tags: Male
Adult
Creatine Kinase: BL, blood
Cystic Fibrosis: PP, physiopathology
***Cystic Fibrosis: SU, surgery**
Forced Expiratory Volume
Humans
Hydrocortisone: BL, blood
*Lung Transplantation
Research Support, Non-U.S. Gov't

*Running
Running: PH, physiology
Uric Acid: BL, blood
CAS REGISTRY NO.: 50-23-7 (Hydrocortisone); 69-93-2 (Uric Acid)
CHEMICAL NAME: EC 2.7.3.2 (Creatine Kinase)

L148 ANSWER 27 OF 56 MEDLINE on STN
ACCESSION NUMBER: 97339439 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9196038
TITLE: Genistein directly induces cardiac **CFTR** chloride current by a tyrosine kinase-independent and protein kinase A-independent pathway in guinea pig ventricular myocytes.
AUTHOR: Chiang C E; Chen S A; Chang M S; Lin C I; Luk H N
CORPORATE SOURCE: Division of Cardiology, Veterans General Hospital-Taipei and National Yang-Ming University School of Medicine, Taiwan, Republic of China.. cechiang@vghtpe.gov.tw
SOURCE: Biochemical and biophysical research communications, (1997 Jun 9) 235 (1) 74-8.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970805
Last Updated on STN: 19980206
Entered Medline: 19970721

ABSTRACT:
With one-suction electrode voltage-clamp technique, we demonstrated that genistein, a tyrosine kinase (TK) inhibitor, could directly activate ***cystic*** **fibrosis** transmembrane regulator (**CFTR**) chloride current in guinea pig ventricular myocytes. The activation showed concentration-dependent effect with the estimated IC50 of 39.7 microM. Tyrphostin 51, another TK inhibitor, had no effect, suggesting that genistein's effect might be unrelated to TK inhibition. After the chloride current had been activated by the maximally elevated intracellular cAMP content by saturating concentration of isoproterenol, forskolin and IBMX, genistein could further enhance the current. Pre-treatment with saturating concentration of a specific protein kinase A (PKA) inhibitor, H-89, or other protein kinase inhibitors **H-8** and H-9 in the perfusate or intracellularly could not prevent the activation of the current by genistein, suggesting a PKA-independent activity. Furthermore, saturating concentration of calyculin A, a specific inhibitor of phosphotase 1 and 2A, in the perfusate or intracellularly could not block genistein's action. It is possible that genistein opens the channels directly or inhibits the dephosphorylation process of **CFTR**, which is not sensitive calyculin A.

CONTROLLED TERM: Check Tags: Female; Male
Adrenergic beta-Agonists: PD, pharmacology
Animals
Cells, Cultured
Chloride Channels: DE, drug effects
*Chloride Channels: ME, metabolism
Chlorides: ME, metabolism
*Cyclic AMP-Dependent Protein Kinases: ME, metabolism
***Cystic Fibrosis Transmembrane Conductance Regulator: ME, metabolism**
*Enzyme Inhibitors: PD, pharmacology
Forskolin: PD, pharmacology
Genistein
Guinea Pigs

Heart Ventricles: DE, drug effects
*Isoflavones: PD, pharmacology
Isoproterenol: PD, pharmacology
Isoquinolines: PD, pharmacology
*Myocardium: ME, metabolism
Oxazoles: PD, pharmacology
Patch-Clamp Techniques
Protein-Tyrosine Kinase: AI, antagonists & inhibitors
*Protein-Tyrosine Kinase: ME, metabolism
Research Support, Non-U.S. Gov't
*Sulfonamides
CAS REGISTRY NO.: 101932-71-2 (calyculin A); **126880-72-6 (Cystic Fibrosis Transmembrane Conductance Regulator)**; 127243-85-0 (H 89); 446-72-0 (Genistein); 486-66-8 (daidzein); 66428-89-5 (Forskolin); 7683-59-2 (Isoproterenol)
CHEMICAL NAME: 0 (Adrenergic beta-Agonists); 0 (Chloride Channels); 0 (Chlorides); 0 (Enzyme Inhibitors); 0 (Isoflavones); 0 (Isoquinolines); 0 (Oxazoles); 0 (Sulfonamides); EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 2.7.1.37 (Cyclic AMP-Dependent Protein Kinases)

L148 ANSWER 28 OF 56 MEDLINE on STN
ACCESSION NUMBER: 96088787 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7576703
TITLE: **CFTR**-mediated chloride permeability is regulated by type III phosphodiesterases in airway epithelial cells.
AUTHOR: Kelley T J; al-Nakkash L; Drumm M L
CORPORATE SOURCE: Department of Pediatrics, Willard Bernbaum Cystic Fibrosis Center, USA.
CONTRACT NUMBER: DK45965 (NIDDK)
P30 DK27651 (NIDDK)
T32 HL07451 (NHLBI)
SOURCE: American journal of respiratory cell and molecular biology, (1995 Dec) 13 (6) 657-64.
Journal code: 8917225. ISSN: 1044-1549.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951228

ABSTRACT:
Chloride channel activity of **cystic fibrosis** transmembrane conductance regulator (**CFTR**) requires activation of protein kinase A (PKA) by 3'-5'-cyclic adenosine monophosphate (cAMP). The level of cAMP is controlled by the balance between cAMP synthesis and hydrolysis by adenylate cyclase and phosphodiesterases (PDEs), respectively. **CFTR** channel activity appears to be most sensitive to the activity of type III cyclic nucleotide PDEs in Calu-3 and 16HBE cells, both derived from airway epithelium and expressing wild-type **CFTR.** Type III PDEs can be identified by their sensitivity to specific inhibitors such as milrinone and amrinone. In Calu-3 cells, specific inhibition of type III PDEs increased chloride efflux up to 13.7-fold, whereas neither rolipram nor Ro20-1724 (type IV PDE inhibitors) nor 3-isobutyl-1-methylxanthine (IBMX, a nonspecific PDE inhibitor) elicited significant increases. None of these compounds had an appreciable effect on total cellular cAMP levels, yet the effects of milrinone and amrinone on chloride efflux were blocked by treatment of cells with Rp-cAMPS, a cAMP analog

that inhibits PKA at the site of cAMP binding. Similarly, **H-***8*** , an inhibitor of PKA, reduced milrinone-stimulated chloride efflux, indicating that efflux is mediated through the cAMP/PKA pathway. Whole-cell patch clamp analysis revealed that milrinone generated chloride conductances with properties consistent with those of **CFTR.** Milrinone elicited chloride currents in a dose-dependent manner and induced **CFTR** activity in the absence of adenylate cyclase agonists. These data suggest that type III PDEs are specifically involved in **CFTR** activation in airway epithelial cells and that PDE regulation of **CFTR** may involve subcellular compartments of cAMP.

CONTROLLED TERM: Cell Line
Cell Membrane Permeability: PH, physiology
Cell Polarity: PH, physiology
*Chloride Channels: PH, physiology
*Chlorides: PK, pharmacokinetics
Cyclic AMP: ME, metabolism
***Cystic Fibrosis Transmembrane Conductance Regulator: PH, physiology**
Epithelium: ME, metabolism
Humans
Lung: CY, cytology
Patch-Clamp Techniques
Phosphodiesterase Inhibitors: PD, pharmacology
*Phosphoric Diester Hydrolases: PH, physiology
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.

CAS REGISTRY NO.: **126880-72-6 (Cystic Fibrosis Transmembrane Conductance Regulator)**; 60-92-4 (Cyclic AMP)

CHEMICAL NAME: 0 (Chloride Channels); 0 (Chlorides); 0 (Phosphodiesterase Inhibitors); EC 3.1.4 (Phosphoric Diester Hydrolases)

L148 ANSWER 29 OF 56 MEDLINE on STN
ACCESSION NUMBER: 92272145 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1317106
TITLE: cGMP-dependent protein kinase regulation of a chloride channel in T84 cells.
AUTHOR: Lin M; Nairn A C; Guggino S E
CORPORATE SOURCE: Department of Medicine, Johns Hopkins University, School of Medicine, Baltimore, Maryland 21205.
SOURCE: American journal of physiology, (1992 May) 262 (5 Pt 1) C1304-12.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199206
ENTRY DATE: Entered STN: 19920710
Last Updated on STN: 19970203
Entered Medline: 19920625

ABSTRACT:
Chloride channels at the apical membrane of intestinal epithelial cells are involved in the excessive fluid secretion in diarrhea and diminished secretion in **cystic fibrosis** (CF). Diarrhea induced by heat-stable toxin from Escherichia coli is associated with elevated guanosine 3',5'-cyclic monophosphate (cGMP) in intestinal epithelial cells, but it is unknown whether chloride secretion is regulated by cGMP directly or via cGMP-dependent protein kinase (PKG). Single-channel recordings (inside-out excised patches) from the apical membrane of T84 cells reveal a 10-pS chloride channel with a linear current-voltage relationship, which is opened when an endogenous membrane-bound

PKG is activated with ATP (1 mM) and cGMP (100 microM). Soluble PKG (200 nM) isolated from bovine lung, added to the intracellular face of patches, also opens this channel. No activation occurs with Ringer solution alone or only ATP or cGMP. Addition of nonhydrolyzable forms of ATP (AMP-PNP, 1 mM) or a combination of ATP, cGMP, plus **H-8** (5 microM), an inhibitor of PKG, also does not stimulate the channel. The catalytic subunit of adenosine 3',5'-cyclic mono-phosphate-dependent protein kinase (PKA, 200 nM, with 1 mM ATP) activates a channel with similar characteristics. The 10 pS channel has a PNa/PCl ratio of 0.06, an anion selectivity of Br- (1.2) greater than Cl- (1.0) greater than I- (0.8) greater than F- (0.4), and a low affinity for the chloride channel blockers, 4,4-dinitrostilbene-2,2-disulfonic acid and 5-nitro-2-(3-phenylpropylamino)benzoic acid.(ABSTRACT TRUNCATED AT 250 WORDS)

CONTROLLED TERM: Adenosine Triphosphate: PD, pharmacology
*Carcinoma: ME, metabolism
Chloride Channels
Chlorides: ME, metabolism
*Colonic Neoplasms: ME, metabolism
Cyclic GMP: PD, pharmacology
*Cyclic GMP: PH, physiology
Electric Conductivity
Humans
Ion Channel Gating
Membrane Proteins: AI, antagonists & inhibitors
*Membrane Proteins: ME, metabolism
Membrane Proteins: PH, physiology
Nitrobenzoates: PD, pharmacology
*Protein Kinases: PH, physiology
Research Support, Non-U.S. Gov't
Stilbenes: PD, pharmacology
Tumor Cells, Cultured

CAS REGISTRY NO.: 107254-86-4 (5-nitro-2-(3-phenylpropylamino)benzoic acid); 128-42-7 (4,4'-dinitro-2,2'-stilbenedisulfonic acid); 56-65-5 (Adenosine Triphosphate); 7665-99-8 (Cyclic GMP)

CHEMICAL NAME: 0 (Chloride Channels); 0 (Chlorides); 0 (Membrane Proteins); 0 (Nitrobenzoates); 0 (Stilbenes); EC 2.7.1.37 (Protein Kinases)

L148 ANSWER 30 OF 56 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005275082 EMBASE

TITLE: The favorable outcome of human islet transplantation in Korea: Experiences of 10 autologous transplantations.

AUTHOR: Lee B.-W.; Jee J.-H.; Heo J.-S.; Choi S.-H.; Jang K.-T.; Noh J.-H.; Jeong I.-K.; Oh S.-H.; Ahn Y.-R.; Chae H.-Y.; Min Y.-K.; Chung J.-H.; Lee M.-K.; Lee M.-S.; Kim K.-W.

CORPORATE SOURCE: Dr. K.-W. Kim, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Ilwondong, Kangnam-ku, Seoul 135-710, Korea, Republic of. kwwkim@smc.samsung.co.kr

SOURCE: Transplantation, (15 Jun 2005) Vol. 79, No. 11, pp. 1568-1574. .
Refs: 31
ISSN: 0041-1337 CODEN: TRPLAU

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050707

Last Updated on STN: 20050707

ABSTRACT: Background. **Cystic** neoplasms of the pancreas are an increasingly diagnosed entity, and surgical resection of the pancreas is advocated. Islet autotransplantation is a therapeutic approach used to prevent diabetes in cases of pathologically benign neoplasm after major pancreatectomy. Methods. A total of 10 patients underwent pancreatectomy with islet autotransplantation. To evaluate islet transplantation efficiency, the authors compared 23 subjects who did not undergo islet transplantation after partial pancreatectomy with 87 subjects with normal glucose tolerance and with 77 diabetic subjects that did not undergo pancreatectomy. Results. Ten female patients with nine **cystic** neoplasms and one patient with pancreatic injury underwent transplantation. Their mean islet equivalents (IEQ) was 3,159 IEQ/kg. During follow-up, two recipients required insulin or oral agents. At the 12-month follow-up, homeostasis model assessment (HOMA)-β was 77.36 ± 17.68, the insulinogenic index (INSindex) was 0.49 ± 0.11, and fasting C-peptide and hemoglobin A1c were 1.28 ± 0.18 ng/mL and 5.73 ± 0.26%, respectively. Islet replacement was found to increase HOMA-β by approximately 17% compared with distal pancreatectomy in normal glucose tolerance subjects without islet autotransplantation and by 46% compared with distal pancreatectomy diabetes subjects without islet autotransplantation. Factors different in the two insulin and oral hypoglycemic agent (OHA)-requiring recipients and the eight insulin- and OHA-free recipients were pancreatectomy extent, preoperative glucose metabolism insufficiency, age, and underlying **cystic** neoplasm disease. Conclusions. Even partial islet graft function can have a beneficial metabolic effect on the recipient in terms of metabolic parameters such as HOMA-β and INSindex. This study suggests that islet replacement should be considered for experimental procedures in benign pancreatic conditions. Copyright .COPYRGT. 2005 by Lippincott Williams & Wilkins.

CONTROLLED TERM: Medical Descriptors:
*pancreas islet transplantation
*autotransplantation
South Korea
pancreas cyst: DI, diagnosis
pancreas cyst: SU, surgery
diabetes mellitus
pancreas resection
evaluation
glucose tolerance
pancreas injury: SU, surgery
follow up
homeostasis
model
homeostasis model assessment beta assay
assay
outcomes research
glucose metabolism
human
female
clinical article
controlled study
adult
article
priority journal
Drug Descriptors:
insulin: DO, drug dose
metformin: DO, drug dose
metformin: PO, oral drug administration
rosiglitazone: DO, drug dose

rosiglitazone: PO, oral drug administration
oral antidiabetic agent: DO, drug dose
oral antidiabetic agent: PO, oral drug administration
CAS REGISTRY NO.: (insulin) 9004-10-8; (metformin) 1115-70-4, 657-24-9; (**rosiglitazone**) **122320-73-4, 155141-29-0**

L148 ANSWER 31 OF 56 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005106462 EMBASE
TITLE: Therapeutic effects of **troglitazone** in experimental chronic pancreatitis in mice.
AUTHOR: Van Westerloo D.J.; Florquin S.; De Boer A.M.; Daalhuisen J.; De Vos A.F.; Bruno M.J.; Van Der Poll T.
CORPORATE SOURCE: Dr. D.J. Van Westerloo, Academic Medical Center, Dept. of Gastroenterol. and Hepatol., Meibergdreef 9, 1105 AZ, Amsterdam, Netherlands. d.j.vanwesterloo@amc.uva.nl
SOURCE: American Journal of Pathology, (2005) Vol. 166, No. 3, pp. 721-728. .
Refs: 41
ISSN: 0002-9440 CODEN: AJPAA4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050324
Last Updated on STN: 20050324

ABSTRACT: Peroxisome proliferator-activated receptor (PPAR)-γ controls growth, differentiation, and inflammation. PPAR-γ agonists exert anti-inflammatory effects in vitro and inhibit the activation of pancreas stellate cells, implicated in the formation and progression of fibrosis. We determined the influence of **troglitazone**, a ligand for PPAR-γ, on pancreatic damage and fibrosis in experimental chronic pancreatitis. Mice received six hourly intraperitoneal injections with 50 μg/kg of cerulein or saline, three times a week for 6 weeks. One week after the last injection all mice were sacrificed. Untreated mice were compared with mice treated with ***troglitazone*** either during weeks 1 to 6 or weeks 4 to 6. All mice that received cerulein injections displayed histopathological signs of chronic pancreatitis at week 7. **Troglitazone** treatment improved all markers for severity of pancreatitis. Moreover, early and postponed ***troglitazone*** treatments were equally effective in diminishing intrapancreatic fibrosis as quantified by Sirius red staining, hydroxyproline content, and laminin staining as well as the increased number of pancreatic stellate cells and pancreas levels of transforming growth factor-β. Thus, ***troglitazone*** attenuated pancreatic damage and inflammation in experimental chronic pancreatitis and remained beneficial in a therapeutic setting when given after initial damage had been established. Copyright .COPYRGT. American Society for Investigative Pathology.

CONTROLLED TERM: Medical Descriptors:
*chronic pancreatitis: DT, drug therapy
drug effect
antiinflammatory activity
cystic fibrosis: DT, drug therapy
pancreas injury: DT, drug therapy
histopathology

disease severity
stellate cell
enzyme linked immunosorbent assay
immunohistochemistry
enzyme activity
nonhuman
female
mouse
animal model
controlled study
animal tissue
article
priority journal
Drug Descriptors:
***troglitazone: DO, drug dose**
***troglitazone: DT, drug therapy**
***troglitazone: PD, pharmacology**
***troglitazone: PO, oral drug administration**
peroxisome proliferator activated receptor gamma: EC, endogenous compound
peroxisome proliferator activated receptor agonist
ceruletide
sodium chloride
hydroxyproline: EC, endogenous compound
transforming growth factor beta1: EC, endogenous compound
collagen: EC, endogenous compound
interleukin 6: EC, endogenous compound
tumor necrosis factor receptor 1: EC, endogenous compound
myeloperoxidase: EC, endogenous compound
laminin: EC, endogenous compound
alpha smooth muscle actin: EC, endogenous compound
amylase: EC, endogenous compound

CAS REGISTRY NO.: (**troglitazone**) **97322-87-7**; (ceruletide) 17650-98-5; (sodium chloride) 7647-14-5; (hydroxyproline) 51-35-4, 6912-67-0; (collagen) 9007-34-5; (laminin) 2408-79-9; (amylase) 9000-90-2, 9000-92-4, 9001-19-8

COMPANY NAME: Sankyo (Japan)

L148 ANSWER 32 OF 56 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005403676 EMBASE
TITLE: Emerging therapies for polycystic kidney disease.
AUTHOR: Gattone II V.H.
CORPORATE SOURCE: V.H. Gattone II, Department of Anatomy and Cell Biology, Indiana University School of Medicine, Indianapolis, IN 46202, United States. vgattone@iupui.edu
SOURCE: Current Opinion in Pharmacology, (2005) Vol. 5, No. 5 SPEC.ISS., pp. 535-542. .
Refs: 85
ISSN: 1471-4892 CODEN: COPUBK
PUBLISHER IDENT.: S 1471-4892(05)00114-1
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 022 Human Genetics
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050922

Last Updated on STN: 20050922

ABSTRACT: Polycystic kidney diseases are the most common, monogenetic, inherited diseases in humans. Numerous human genes or gene loci are associated with a renal **cystic** phenotype. Currently, there are no treatments available to slow the development of renal **cystic** pathology; however, animal studies have identified several potential approaches to intervene in the disease process. The most advanced therapy is the use of vasopressin V(2) receptor antagonists, which reduce renal cAMP, a known promoter of renal ***cystic*** enlargement. Other therapies under study include the use of c-myc antisense oligonucelotides and epidermal growth factor receptor tyrosine kinase inhibitors. Considering the diverse genes that cause renal cysts and the multiorgan involvement of these diseases, multiple therapeutic approaches will eventually be necessary to treat these diseases. .COPYRGT. 2005 Elsevier Ltd. All rights reserved.

CONTROLLED TERM: Medical Descriptors:
*kidney polycystic disease: DT, drug therapy
*kidney polycystic disease: ET, etiology
*kidney polycystic disease: TH, therapy
monogenic disorder
gene locus
phenotype
genetic association
disease control
pathology
disease course
drug mechanism
kidney cyst
gene therapy
drug screening
human
nonhuman
clinical trial
review
priority journal
Drug Descriptors:
vasopressin V2 receptor: EC, endogenous compound
vasopressin receptor antagonist: CM, drug comparison
vasopressin receptor antagonist: DV, drug development
vasopressin receptor antagonist: DT, drug therapy
vasopressin receptor antagonist: PD, pharmacology
cyclic AMP: EC, endogenous compound
Myc protein: EC, endogenous compound
mozavaptan: DV, drug development
mozavaptan: DT, drug therapy
mozavaptan: PD, pharmacology
tolvaptan: CT, clinical trial
tolvaptan: DT, drug therapy
tolvaptan: PD, pharmacology
small interfering RNA: DV, drug development
small interfering RNA: DT, drug therapy
antisense oligonucleotide: CT, clinical trial
antisense oligonucleotide: CM, drug comparison
antisense oligonucleotide: DT, drug therapy
antisense oligonucleotide: PD, pharmacology
avi 4126: CT, clinical trial
avi 4126: CM, drug comparison
avi 4126: DT, drug therapy
avi 4126: PD, pharmacology
epidermal growth factor receptor kinase inhibitor: CM, drug

comparison
epidermal growth factor receptor kinase inhibitor: DT, drug therapy
chlorotrianisene: CM, drug comparison
chlorotrianisene: DV, drug development
chlorotrianisene: DT, drug therapy
chlorotrianisene: PD, pharmacology
paclitaxel: CM, drug comparison
paclitaxel: DV, drug development
paclitaxel: DT, drug therapy
paclitaxel: PD, pharmacology
dipeptidyl carboxypeptidase inhibitor: CM, drug comparison
dipeptidyl carboxypeptidase inhibitor: DT, drug therapy
dipeptidyl carboxypeptidase inhibitor: PD, pharmacology
angiotensin receptor antagonist: DT, drug therapy
angiotensin receptor antagonist: PD, pharmacology
methylprednisolone: CM, drug comparison
methylprednisolone: DT, drug therapy
methylprednisolone: PD, pharmacology
rapamycin: CM, drug comparison
rapamycin: DT, drug therapy
matrix metalloproteinase inhibitor: CM, drug comparison
matrix metalloproteinase inhibitor: DT, drug therapy
matrix metalloproteinase inhibitor: PD, pharmacology
antilipemic agent: CM, drug comparison
antilipemic agent: DT, drug therapy
pioglitazone: CM, drug comparison
pioglitazone: DT, drug therapy
octreotide: DT, drug therapy
cyclooxygenase 2 inhibitor: DT, drug therapy
unclassified drug

CAS REGISTRY NO.: (cyclic AMP) 60-92-4; (mozavaptan) 137975-06-5; (tolvaptan) 150683-30-0; (chlorotrianisene) 569-57-3; (paclitaxel) 33069-62-4; (methylprednisolone) 6923-42-8, 83-43-2; (rapamycin) 53123-88-9; (**pioglitazone**) **105355-27-9, 111025-46-8**; (octreotide) 83150-76-9

CHEMICAL NAME: (1) Avi 4126; Opc 31260; Opc 41061

COMPANY NAME: (1) Avi Biopharma

L148 ANSWER 33 OF 56 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005372852 EMBASE

TITLE: Emerging role of AMP-activated protein kinase in coupling membrane transport to cellular metabolism.

AUTHOR: Hallows K.R.

CORPORATE SOURCE: Dr. K.R. Hallows, Renal-Electrolyte Division, Department of Medicine, University of Pittsburgh School of Medicine, 3550 Terrace Street, Pittsburgh, PA 15261, United States. hallows@pitt.edu

SOURCE: Current Opinion in Nephrology and Hypertension, (2005) Vol. 14, No. 5, pp. 464-471. .
Refs: 73
ISSN: 1062-4821 CODEN: CNHYEM

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 002 Physiology
029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20050915
Last Updated on STN: 20050915

ABSTRACT: Purpose of review: It has long been recognized that the coupling of membrane transport to underlying cellular metabolic status is critical because transport processes consume a large portion of total cellular energy. Recently, the finely tuned metabolic sensor AMP-activated protein kinase (AMPK) has emerged as a membrane transport regulator, which may permit sensitive transport-metabolism crosstalk. This review will discuss how AMPK may play an important role in the regulation of ion and solute transport across the plasma membrane under both physiological and pathological conditions in epithelia and other tissues. Recent findings: Recent studies have found that AMPK, which becomes activated during cellular metabolic stress, promotes the cellular uptake of fuel sources such as glucose and fatty acids to promote ATP generation and inhibits ion-transport proteins such as the **cystic** fibrosis transmembrane conductance regulator Cl(-) channel and the epithelial Na(+) channel, thereby limiting the dissipation of transmembrane ion gradients. An understanding of the underlying cellular and molecular mechanisms for AMPK-dependent regulation of transport proteins is beginning to emerge. Summary: As earlier studies have focused on the role of nucleotides such as ATP in regulating transport-protein activities, the regulation of membrane transport by AMPK represents a novel and more-sensitive mechanism for the coupling of membrane transport to cellular metabolic status. Identifying new membrane-transport targets of AMPK and elucidating the mechanisms involved in their AMPK-dependent regulation are fruitful areas for new investigation that should yield valuable insights into the pathophysiology of hypoxic and ischemic tissue injury. .COPYRGT. 2005 Lippincott Williams & Wilkins.

CONTROLLED TERM: Medical Descriptors:
*membrane transport
*cell metabolism
regulatory mechanism
ion transport
solute
chloride channel
hypoxia
ischemia
tissue injury
nutrient uptake
voltage gated sodium channel
familial hypertrophic cardiomyopathy
Wolff Parkinson White syndrome
Peutz Jeghers syndrome
Xenopus
oocyte
pancreas islet beta cell
glucose transport
fatty acid transport
cell growth
inflammation
protein synthesis
glycogen synthesis
fatty acid synthesis
sterol synthesis
oxidative stress
nonhuman
mouse
controlled study
animal cell
review
priority journal

Drug Descriptors:
*hydroxymethylglutaryl coenzyme A reductase kinase: EC, endogenous compound
glucose: EC, endogenous compound
fatty acid: EC, endogenous compound
adenosine triphosphate: EC, endogenous compound
transmembrane conductance regulator: EC, endogenous compound
sodium potassium chloride cotransporter: EC, endogenous compound
adenosine triphosphatase (potassium sodium): EC, endogenous compound
metformin
rosiglitazone
mammalian target of rapamycin: EC, endogenous compound
apoptosis signal regulating kinase 1: EC, endogenous compound
5 amino 4 imidazolecarboxamide riboside
glucose transporter 1: EC, endogenous compound
glucose transporter 2: EC, endogenous compound
sodium glucose cotransporter 1: EC, endogenous compound
ubiquitin protein ligase NEDD4: EC, endogenous compound

CAS REGISTRY NO.: (hydroxymethylglutaryl coenzyme A reductase kinase) 172522-01-9, 72060-32-3; (glucose) 50-99-7, 84778-64-3; (adenosine triphosphate) 15237-44-2, 56-65-5, 987-65-5; (metformin) 1115-70-4, 657-24-9; (**rosiglitazone**) **122320-73-4**, **155141-29-0**; (apoptosis signal regulating kinase 1) 185464-61-3; (5 amino 4 imidazolecarboxamide riboside) 2627-69-2; (glucose transporter 1) 172077-08-6; (glucose transporter 2) 357693-20-0

L148 ANSWER 34 OF 56 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005402165 EMBASE
TITLE: Anti-inflammatory medications for **cystic** fibrosis lung disease: Selecting the most appropriate agent.
AUTHOR: Chmiel J.F.; Konstan M.W.
CORPORATE SOURCE: J.F. Chmiel, Division of Pediatric Pulmonology, MS# 6006, Rainbow Babies and Children's Hospital, 11100 Euclid Avenue, Cleveland, OH 44106, United States. james.chmiel@uhhs.com
SOURCE: Treatments in Respiratory Medicine, (2005) Vol. 4, No. 4, pp. 255-273. .
Refs: 161
ISSN: 1176-3450 CODEN: TRMRCZ
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
015 Chest Diseases, Thoracic Surgery and Tuberculosis
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20051006
Last Updated on STN: 20051006

ABSTRACT: The lung disease of **cystic** fibrosis (CF) is characterized by a self-sustaining cycle of airway obstruction, infection, and inflammation. Therapies aimed at decreasing the inflammatory response represent a relatively

new strategy for treatment. Attention has focused primarily upon the therapeutic potential of corticosteroids and NSAIDs. Although beneficial, the use of systemic corticosteroids is limited by their unacceptable adverse effects. It is unclear if inhaled corticosteroids are a viable alternative, although their use in CF has dramatically increased in recent years. High-dose ibuprofen has been shown to slow progression of CF lung disease, but its use has not been widely adopted despite a favorable risk-benefit profile. Thus, other anti-inflammatory approaches are under investigation. Since the inflammatory response can be triggered by many stimuli and since the pathways activated by these stimuli produce many mediators, there are a plethora of targets for anti-inflammatory therapeutics. Specific antibodies, receptor antagonists, and counter-regulatory cytokines, such as interleukin (IL)-10 and interferon-γ inhibit the pro-inflammatory mediators responsible for the damaging inflammation in the CF airway, including tumor necrosis factor-α, IL-1β and IL-8. Studies of molecules that modulate intracellular signaling cascades that lead to the production of inflammatory mediators, are underway in CF. For patients with established disease, recent and projected advances in therapies that are directed at neutrophil products, such as DNase, antioxidants, and protease inhibitors, hold great promise for limiting the consequences of the inflammatory response. To optimize anti-inflammatory therapy, it is necessary to understand the mechanism of action of these agents in the CF lung to determine which agents will be most beneficial, and to determine which therapies should be initiated at what age and stage of lung disease. Hope remains that correction of the abnormal CF transmembrane conductance regulator protein or gene replacement therapy will be curative. However, correction of the basic defect must also correct the dysregulated inflammatory response in order to be effective. Until those therapies aimed at repairing the basic defect are realized, limiting the effects of the inflammatory process will be important in slowing the decline in lung function and thus prolonging survival in patients with CF.

CONTROLLED TERM: Medical Descriptors:
***cystic fibrosis: DT, drug therapy**
airway obstruction
respiratory tract infection: DT, drug therapy
pneumonia
drug use
drug megadose
disease course
health hazard
stimulus
drug targeting
antibody specificity
lung injury
signal transduction
neutrophil
age
gene replacement therapy
convalescence
lung function
survival time
Staphylococcus infection: ET, etiology
Staphylococcus aureus
Gram negative infection: DT, drug therapy
Gram negative infection: ET, etiology
Gram negative infection: PC, prevention
Haemophilus influenzae type a
Pseudomonas aeruginosa
Burkholderia cepacia

Stenotrophomonas maltophilia
Achromobacter xylosoxidans
bacterial infection: DT, drug therapy
bacterial infection: ET, etiology
bacterial infection: PC, prevention
growth retardation: SI, side effect
cataract: SI, side effect
disorders of carbohydrate metabolism: SI, side effect
glucose intolerance: SI, side effect
disease exacerbation: DT, drug therapy
disease exacerbation: SI, side effect
osteopenia
osteoporosis
muscle weakness: SI, side effect
bone density
side effect: SI, side effect
epistaxis: SI, side effect
conjunctivitis: SI, side effect
gastrointestinal symptom: DT, drug therapy
gastrointestinal symptom: SI, side effect
gastrointestinal hemorrhage: DT, drug therapy
gastrointestinal hemorrhage: SI, side effect
kidney failure: SI, side effect
bronchiectasis: DT, drug therapy
bronchiolitis: DT, drug therapy
nausea: SI, side effect
diarrhea: SI, side effect
wheezing: SI, side effect
kidney dysfunction: SI, side effect
hypertrichosis: SI, side effect
gingiva hyperplasia: SI, side effect
drug safety
human
nonhuman
clinical trial
review
priority journal
Drug Descriptors:
*antiinflammatory agent: AE, adverse drug reaction
*antiinflammatory agent: CT, clinical trial
*antiinflammatory agent: CB, drug combination
*antiinflammatory agent: CM, drug comparison
*antiinflammatory agent: CR, drug concentration
*antiinflammatory agent: DO, drug dose
*antiinflammatory agent: DT, drug therapy
*antiinflammatory agent: IH, inhalational drug administration
***antiinflammatory agent: PO, oral drug administration**
*antiinflammatory agent: PK, pharmacokinetics
*antiinflammatory agent: PD, pharmacology
corticosteroid: AE, adverse drug reaction
corticosteroid: CT, clinical trial
corticosteroid: CM, drug comparison
corticosteroid: DO, drug dose
corticosteroid: DT, drug therapy
corticosteroid: IH, inhalational drug administration
corticosteroid: PO, oral drug administration
corticosteroid: PD, pharmacology
prednisone: DO, drug dose

prednisone: DT, drug therapy
prednisone: PO, oral drug administration
nonsteroid antiinflammatory agent: AE, adverse drug reaction
nonsteroid antiinflammatory agent: CT, clinical trial
nonsteroid antiinflammatory agent: CM, drug comparison
nonsteroid antiinflammatory agent: CR, drug concentration
nonsteroid antiinflammatory agent: DO, drug dose
nonsteroid antiinflammatory agent: DT, drug therapy
nonsteroid antiinflammatory agent: PO, oral drug administration
nonsteroid antiinflammatory agent: PD, pharmacology
ibuprofen: AE, adverse drug reaction
ibuprofen: CT, clinical trial
ibuprofen: CB, drug combination
ibuprofen: CR, drug concentration
ibuprofen: DO, drug dose
ibuprofen: DT, drug therapy
ibuprofen: PO, oral drug administration
ibuprofen: PD, pharmacology
antacid agent: CB, drug combination
antacid agent: DT, drug therapy
proton pump inhibitor: CB, drug combination
proton pump inhibitor: DT, drug therapy
misoprostol: CB, drug combination
misoprostol: DT, drug therapy
piroxicam: CT, clinical trial
piroxicam: DT, drug therapy
piroxicam: PD, pharmacology
celecoxib: PD, pharmacology
etanercept: PD, pharmacology
infliximab: DT, drug therapy
interleukin 8 antibody: DV, drug development
interleukin 10: CT, clinical trial

CONTROLLED TERM: Drug Descriptors:
interleukin 10: DT, drug therapy
interleukin 10: PD, pharmacology
gamma interferon: AE, adverse drug reaction
gamma interferon: CT, clinical trial
gamma interferon: DO, drug dose
gamma interferon: DT, drug therapy
gamma interferon: IH, inhalational drug administration
gamma interferon: PD, pharmacology
2,4 thiazolidinedione derivative: PD, pharmacology
hydroxymethylglutaryl coenzyme A reductase inhibitor: CT, clinical trial
hydroxymethylglutaryl coenzyme A reductase inhibitor: DT, drug therapy
hydroxymethylglutaryl coenzyme A reductase inhibitor: PD, pharmacology
zileuton: DT, drug therapy
zileuton: PD, pharmacology
amelubant: CT, clinical trial
docosahexaenoic acid: DT, drug therapy
docosahexaenoic acid: PO, oral drug administration
docosahexaenoic acid: PD, pharmacology
antioxidant: CT, clinical trial
antioxidant: CR, drug concentration
antioxidant: DO, drug dose
antioxidant: DT, drug therapy

antioxidant: PD, pharmacology
beta carotene: CT, clinical trial
beta carotene: CR, drug concentration
beta carotene: DT, drug therapy
beta carotene: PO, oral drug administration
beta carotene: PD, pharmacology
alpha tocopherol: CR, drug concentration
alpha tocopherol: DO, drug dose
alpha tocopherol: DT, drug therapy
alpha tocopherol: PD, pharmacology
proteinase inhibitor: CT, clinical trial
proteinase inhibitor: DO, drug dose
proteinase inhibitor: DT, drug therapy
proteinase inhibitor: PK, pharmacokinetics
proteinase inhibitor: PD, pharmacology
alpha 1 antitrypsin: CT, clinical trial
alpha 1 antitrypsin: DO, drug dose
alpha 1 antitrypsin: DT, drug therapy
alpha 1 antitrypsin: PK, pharmacokinetics
alpha 1 antitrypsin: PD, pharmacology
mucolytic agent: CT, clinical trial
mucolytic agent: DT, drug therapy
mucolytic agent: PD, pharmacology
antibiotic agent: AE, adverse drug reaction
antibiotic agent: CT, clinical trial
antibiotic agent: DT, drug therapy
antibiotic agent: PK, pharmacokinetics
antibiotic agent: PD, pharmacology
pentoxifylline: DT, drug therapy
pentoxifylline: PD, pharmacology
cyclosporin: AE, adverse drug reaction
cyclosporin: DO, drug dose
unindexed drug
unclassified drug
biil 284
n [1 (1,3 benzodioxol 5 yl)butyl] 3,3 diethyl 2 [4 [(4 methyl 1 piperazinyl)carbonyl]phenoxy] 4 oxo 1 azetidinecarboxamide

CAS REGISTRY NO.: (prednisone) 53-03-2; (ibuprofen) 15687-27-1; (misoprostol) 59122-46-2, 59122-48-4; (piroxicam) 36322-90-4; (celecoxib) 169590-42-5; (etanercept) 185243-69-0, 200013-86-1; (infliximab) 170277-31-3; (gamma interferon) 82115-62-6; (zileuton) 111406-87-2, 132880-11-6; (docosahexaenoic acid) 25167-62-8, 32839-18-2; (beta carotene) 7235-40-7; (alpha tocopherol) 1406-18-4, 1406-70-8, 52225-20-4, 58-95-7, 59-02-9; (proteinase inhibitor) 37205-61-1; (alpha 1 antitrypsin) 9041-92-3; (pentoxifylline) 6493-05-6; (cyclosporin) 79217-60-0; (n [1 (1,3 benzodioxol 5 yl)butyl] 3,3 diethyl 2 [4 [(4 methyl 1 piperazinyl)carbonyl]phenoxy] 4 oxo 1 azetidinecarboxamide) 157341-41-8

CHEMICAL NAME: Biil 284; L 694458

L148 ANSWER 35 OF 56 EMBASE

ACCESSION NUMBER: 2005309597 EMBASE

TITLE: Diabetes: A major co-morbidity of **cystic** fibrosis.

AUTHOR: Costa M.; Potvin S.; Berthiaume Y.; Gauthier L.; Jeanneret A.; Lavoie A.; Levesque R.; Chiasson J.L.; Rabasa-Lhoret R.

CORPORATE SOURCE: R. Rabasa-Lhoret, Division of Endocrinology Research Center, CHUM Hotel-Dieu, 3850 Saint-Urbain St., Montreal, Que. H2W 1T7. remi.rabasa-lhoret@umontreal.ca
SOURCE: Diabetes and Metabolism, (2005) Vol. 31, No. 3 I, pp. 221-232. .
Refs: 97
ISSN: 1262-3636 CODEN: DIMEFW
COUNTRY: France
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
015 Chest Diseases, Thoracic Surgery and Tuberculosis
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English; French
ENTRY DATE: Entered STN: 20050805
Last Updated on STN: 20050805
ABSTRACT: **Cystic** fibrosis-related diabetes (CFRD) is a frequent complication of **cystic** fibrosis, its prevalence increases with age of patient and is close to 30% at the age of 30 years. As life expectancy greatly increases, the number of **cystic** fibrosis patients developing diabetes will increase too. CFRD shares some features with type 1 and type 2 diabetes, initial phase is characterised by postprandial hyperglycaemia followed by a progression toward insulin deficiency. Insulin deficiency is an essential factor in the development of diabetes with an additional contribution of insulin resistance. Systematic screening with an oral glucose tolerance test is recommended from the age of 14 years because clinical signs of CFRD are often confused with signs of pulmonary infection and CFRD occurrence is associated with weight and pulmonary function deterioration. In observational studies CFRD diagnosis is associated with a significant increase in mortality, while treatment allow correction of weight and lung deterioration suggesting that CFRD has a significant impact on CF evolution. Microvascular complications are recognised, although paucity of data does not permit a clear description of their natural history. Annual screening for microvascular complication is recommended. There is no evidence by now that CF patients develop macrovascular complications. The only recommended pharmacological treatment is insulin therapy.

CONTROLLED TERM: Medical Descriptors:
*diabetes mellitus: CO, complication
*diabetes mellitus: DT, drug therapy
***cystic fibrosis: DT, drug therapy**
***cystic fibrosis: TH, therapy**
comorbidity
prevalence
age
life expectancy
insulin dependent diabetes mellitus
non insulin dependent diabetes mellitus
clinical feature
postprandial state
hyperglycemia
insulin deficiency
disease course
insulin resistance
screening
oral glucose tolerance test
lung infection
deterioration
disease association

weight reduction
mortality
microangiopathy: CO, complication
insulin treatment
hypoglycemia: SI, side effect
liver toxicity: SI, side effect
gastrointestinal symptom
human
adolescent
preschool child
school child
adult
review
Drug Descriptors:
insulin: DT, drug therapy
antibiotic agent: DT, drug therapy
mucolytic agent: DT, drug therapy
antiinflammatory agent: DT, drug therapy
pancreas enzyme: DT, drug therapy
retinol: DT, drug therapy
vitamin D: DT, drug therapy
alpha tocopherol: DT, drug therapy
vitamin K group: DT, drug therapy
isophane insulin: DT, drug therapy
insulin zinc suspension: DT, drug therapy
insulin glargine: DT, drug therapy
repaglinide: DT, drug therapy
tolbutamide: AE, adverse drug reaction
tolbutamide: DT, drug therapy
tolbutamide: PO, oral drug administration
glibenclamide: AE, adverse drug reaction
glibenclamide: DT, drug therapy
glibenclamide: PO, oral drug administration
insulin[B28 lysine B29 proline]: DT, drug therapy
metformin: AE, adverse drug reaction
rosiglitazone: AE, adverse drug reaction
pioglitazone: AE, adverse drug reaction
acarbose: AE, adverse drug reaction

CAS REGISTRY NO.: (insulin) 9004-10-8; (retinol) 68-26-8, 82445-97-4; (alpha tocopherol) 1406-18-4, 1406-70-8, 52225-20-4, 58-95-7, 59-02-9; (vitamin K group) 12001-79-5; (isophane insulin) 9004-17-5; (insulin zinc suspension) 8049-62-5; (insulin glargine) 160337-95-1; (repaglinide) 135062-02-1; (tolbutamide) 473-41-6, 64-77-7; (glibenclamide) 10238-21-8; (insulin[B28 lysine B29 proline]) 133107-64-9; (metformin) 1115-70-4, 657-24-9; (**rosiglitazone**) **122320-73-4**, **155141-29-0**; (**pioglitazone**) **105355-27-9**, **111025-46-8**; (acarbose) 56180-94-0

L148 ANSWER 36 OF 56 EMBASE
ACCESSION NUMBER: 2005492037 EMBASE
TITLE: [**Cystic** fibrosis-related diabetes].
DIABETE DE LA MUCOVISCIDOSE.
AUTHOR: Robert J.-J.
CORPORATE SOURCE: J.-J. Robert, Diabete de l'Enfant et de l'Adolescent, Hopital Necker-Enfants Malades, 149 rue de Sevres, 75743 Paris Cedex 15, France
SOURCE: Medecine Therapeutique Pediatrie, (2005) Vol. 8, No. 3, pp.

217-224. .
Refs: 47
ISSN: 1286-5494 CODEN: MMTPFN
COUNTRY: France
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
015 Chest Diseases, Thoracic Surgery and Tuberculosis
037 Drug Literature Index
LANGUAGE: French
SUMMARY LANGUAGE: French
ENTRY DATE: Entered STN: 20051215
Last Updated on STN: 20051215
CONTROLLED TERM: Medical Descriptors:
***cystic fibrosis: ET, etiology**
*diabetes mellitus: DR, drug resistance
*diabetes mellitus: DT, drug therapy
*diabetes mellitus: ET, etiology
pancreas islet
insulin dependent diabetes mellitus: ET, etiology
autoimmune disease: ET, etiology
hyperglycemia: ET, etiology
microangiopathy: ET, etiology
treatment indication
pathophysiology
pathological anatomy
insulin resistance
pancreas transplantation
human
review
Drug Descriptors:
*insulin: DT, drug therapy
*insulin: PD, pharmacology
sulfanilamide: DT, drug therapy
sulfanilamide: PD, pharmacology
repaglinide: DT, drug therapy
repaglinide: PD, pharmacology
insulin[B28 lysine B29 proline]: DT, drug therapy
insulin[B28 lysine B29 proline]: PD, pharmacology
metformin: DT, drug therapy
metformin: PD, pharmacology
2,4 thiazolidinedione derivative: DT, drug therapy
2,4 thiazolidinedione derivative: PD, pharmacology
CAS REGISTRY NO.: (insulin) 9004-10-8; (sulfanilamide) 34612-79-8, 6101-31-1, 63-74-1; (repaglinide) 135062-02-1; (insulin[B28 lysine B29 proline]) 133107-64-9; (metformin) 1115-70-4, 657-24-9

L148 ANSWER 37 OF 56 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005072801 EMBASE
TITLE: Antifibrotic therapy in chronic liver disease.
AUTHOR: Rockey D.C.
CORPORATE SOURCE: Dr. D.C. Rockey, Sands Building, Box 3083, Duke University Medical Center, Durham, NC 27710, United States. dcrockey@acpub.duke.edu
SOURCE: Clinical Gastroenterology and Hepatology, (2005) Vol. 3, No. 2, pp. 95-107. .
Refs: 123
ISSN: 1542-3565 CODEN: CGHLAW
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 030 Pharmacology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050224
Last Updated on STN: 20050224

ABSTRACT: The response to injury is one of wound healing and, subsequently, fibrosis. This response is generalized, occurring in diverse organ systems. Injury and wounding in the liver ultimately lead to cirrhosis in many patients (although not all patients), and are the result of many different diseases. The fact that various diseases result in cirrhosis suggests a common pathogenesis. Study over the past 2 decades has shed considerable light on the pathogenesis of fibrosis and cirrhosis. A growing body of literature indicates that the hepatic stellate cell is a central component in the fibrogenic process. Stellate cells undergo a transformation during injury that has been termed activation. Activation is complex and multifaceted, but one of its most prominent features is the synthesis of large amounts of extracellular matrix, resulting in deposition of scar or fibrous tissue. The fibrogenic process is dynamic; it is noteworthy that even advanced fibrosis (or cirrhosis) is reversible. The best antifibrotic therapy is treatment of the underlying disease. For example, eradication of hepatitis B or C virus can lead to the reversal of fibrosis. In situations in which treating the underlying process is not possible, specific antifibrotic therapy is desirable. A number of specific antifibrotic therapies have been tried, but have been met with poor or mediocre success. However, elucidation of the mechanisms responsible for fibrogenesis, with particular emphasis on stellate cell biology, has highlighted many putative novel therapies. This article emphasizes mechanisms underlying fibrogenesis, and reviews current antifibrotic therapies as well as potential future approaches.

CONTROLLED TERM: Medical Descriptors:
*chronic liver disease: DT, drug therapy
wound healing
liver fibrosis: DT, drug therapy
liver injury
stellate cell
liver cell
cell transformation
extracellular matrix
scar
fibrogenesis
hepatitis B
eradication therapy
pathophysiology
cell activation
fatty liver: DT, drug therapy
drug potency
drug safety
drug efficacy
liver cirrhosis: DT, drug therapy
primary biliary cirrhosis: DT, drug therapy
alcohol liver cirrhosis: DT, drug therapy
treatment failure
alcohol liver disease: DT, drug therapy
antiviral activity
hepatitis: DR, drug resistance
hepatitis: DT, drug therapy

hepatitis: SI, side effect
chronic hepatitis: SI, side effect
hepatitis C: DR, drug resistance
hepatitis C: DT, drug therapy
infectious hepatitis: DR, drug resistance
infectious hepatitis: DT, drug therapy
side effect: SI, side effect
drug tolerability
drug effect
drug cost
cystic fibrosis: DT, drug therapy
liver toxicity: SI, side effect
infection: SI, side effect
human
nonhuman
clinical trial
review
Drug Descriptors:
*antifibrotic agent: AE, adverse drug reaction
*antifibrotic agent: CT, clinical trial
*antifibrotic agent: CB, drug combination
*antifibrotic agent: CM, drug comparison
*antifibrotic agent: DT, drug therapy
*antifibrotic agent: PO, oral drug administration
*antifibrotic agent: PE, pharmacoeconomics
*antifibrotic agent: PD, pharmacology
*antifibrotic agent: SC, subcutaneous drug administration
lamivudine
ursodeoxycholic acid: CT, clinical trial
ursodeoxycholic acid: DT, drug therapy
ursodeoxycholic acid: PE, pharmacoeconomics
ursodeoxycholic acid: PD, pharmacology
methotrexate: CB, drug combination
methotrexate: DT, drug therapy
methotrexate: PD, pharmacology
peginterferon: CB, drug combination
alpha interferon: CB, drug combination
alpha interferon: CM, drug comparison
antiinflammatory agent: CT, clinical trial
antiinflammatory agent: CB, drug combination
antiinflammatory agent: DT, drug therapy
antiinflammatory agent: PO, oral drug administration
antiinflammatory agent: PD, pharmacology
corticosteroid
rosiglitazone: DT, drug therapy
polyene phosphatidylcholine: CT, clinical trial
polyene phosphatidylcholine: DT, drug therapy
polyene phosphatidylcholine: PD, pharmacology
interleukin 10: CT, clinical trial
interleukin 10: DT, drug therapy
interleukin 10: EC, endogenous compound
interleukin 10: PD, pharmacology
interleukin 10: SC, subcutaneous drug administration
antivirus agent: CB, drug combination
gamma interferon: AE, adverse drug reaction
gamma interferon: CM, drug comparison
gamma interferon: PK, pharmacokinetics
silymarin: CT, clinical trial
silymarin: DT, drug therapy
silymarin: PD, pharmacology

herbaceous agent: AE, adverse drug reaction
herbaceous agent: CT, clinical trial
herbaceous agent: PD, pharmacology
antioxidant: CT, clinical trial
antioxidant: DT, drug therapy
antioxidant: PD, pharmacology
alpha tocopherol: CT, clinical trial
alpha tocopherol: DT, drug therapy
alpha tocopherol: PD, pharmacology
malotilate: PD, pharmacology
s adenosylmethionine: CT, clinical trial
s adenosylmethionine: DT, drug therapy
s adenosylmethionine: PD, pharmacology
propylthiouracil: CT, clinical trial
propylthiouracil: DT, drug therapy
propylthiouracil: PD, pharmacology
oxandrolone: DT, drug therapy
tumor necrosis factor alpha antibody: AE, adverse drug reaction
tumor necrosis factor alpha antibody: PD, pharmacology
dipeptidyl carboxypeptidase inhibitor: PD, pharmacology
angiotensin 2 receptor antagonist: PD, pharmacology
pirfenidone: PD, pharmacology
pentoxifylline: PD, pharmacology
halofuginone: PD, pharmacology
adipocytokine: PD, pharmacology
adiponectin: PD, pharmacology
unindexed drug
unclassified drug

CAS REGISTRY NO.: (lamivudine) 134678-17-4, 134680-32-3; (ursodeoxycholic acid) 128-13-2, 2898-95-5; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (**rosiglitazone**) **122320-73-4, 155141-29-0**; (gamma interferon) 82115-62-6; (silymarin) 65666-07-1; (alpha tocopherol) 1406-18-4, 1406-70-8, 52225-20-4, 58-95-7, 59-02-9; (malotilate) 50512-35-1, 59937-28-9; (s adenosylmethionine) 29908-03-0, 485-80-3; (propylthiouracil) 51-52-5; (oxandrolone) 53-39-4; (pirfenidone) 53179-13-8; (pentoxifylline) 6493-05-6; (halofuginone) 55837-20-2, 64924-67-0, 7695-84-3; (adiponectin) 283182-39-8

L148 ANSWER 38 OF 56 EMBASE

ACCESSION NUMBER: 2005448907 EMBASE

TITLE: The pathophysiological function of peroxisome proliferator-activated receptor-γ in lung-related diseases.

AUTHOR: Huang T.H.-W.; Razmovski-Naumovski V.; Kota B.P.; Lin D.S.-H.; Roufogalis B.D.

CORPORATE SOURCE: Prof. B.D. Roufogalis, Faculty of Pharmacy, University of Sydney, Sydney, NSW 2006, Australia. basilr@pharm.usyd.edu.au

SOURCE: Respiratory Research, (9 Sep 2005) Vol. 6, pp. 9p. .
Refs: 50
ISSN: 1465-993X CODEN: RREEBZ

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
015 Chest Diseases, Thoracic Surgery and Tuberculosis

016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20051027
Last Updated on STN: 20051027

ABSTRACT: Research into respiratory diseases has reached a critical stage and the introduction of novel therapies is essential in combating these debilitating conditions. With the discovery of the peroxisome proliferator-activated receptor and its involvement in inflammatory responses of cardiovascular disease and diabetes, attention has turned to lung diseases and whether knowledge of this receptor can be applied to therapy of the human airways. In this article, we explore the prospect of peroxisome proliferator-activated receptor-γ as a marker and treatment focal point of lung diseases such as asthma, chronic obstructive pulmonary disorder, lung cancer and **cystic** fibrosis. It is anticipated that peroxisome proliferator-activated receptor-γ ligands will provide not only useful mechanistic pathway information but also a possible new wave of therapies for sufferers of chronic respiratory diseases. .COPYRGT. 2005 Huang et al; licensee BioMed Central Ltd.

CONTROLLED TERM: Medical Descriptors:
*lung disease: DT, drug therapy
*lung disease: ET, etiology
pathophysiology
cardiovascular disease
diabetes mellitus
asthma: DT, drug therapy
asthma: ET, etiology
chronic obstructive lung disease: DT, drug therapy
lung cancer: DT, drug therapy
cystic fibrosis
protein expression
in vitro study
human
nonhuman
review
Drug Descriptors:
*peroxisome proliferator activated receptor gamma: EC, endogenous compound
ligand: PD, pharmacology
2,4 thiazolidinedione derivative: CB, drug combination
2,4 thiazolidinedione derivative: CM, drug comparison
2,4 thiazolidinedione derivative: DT, drug therapy
2,4 thiazolidinedione derivative: PD, pharmacology
2,4 thiazolidinedione derivative: NA, intranasal drug administration
2,4 thiazolidinedione derivative: PO, oral drug administration
steroid: CM, drug comparison
steroid: DT, drug therapy
steroid: IH, inhalational drug administration
steroid: PO, oral drug administration
ciglitazone: CB, drug combination
ciglitazone: DT, drug therapy
ciglitazone: PD, pharmacology
farglitazar: CM, drug comparison

farglitazar: DT, drug therapy
farglitazar: PD, pharmacology
farglitazar: NA, intranasal drug administration
peroxisome proliferator activated receptor agonist: CM, drug comparison
peroxisome proliferator activated receptor agonist: PD, pharmacology
2 [4 [2 [3 (2,4 difluorophenyl) 1 heptylureido]ethyl]phenylthio] 2 methylpropionic acid: CM, drug comparison
2 [4 [2 [3 (2,4 difluorophenyl) 1 heptylureido]ethyl]phenylthio] 2 methylpropionic acid: PD, pharmacology
gw 2331: CM, drug comparison
gw 2331: PD, pharmacology
sb 219994: PD, pharmacology
gw 501516: CM, drug comparison
gw 501516: PD, pharmacology
rosiglitazone: CM, drug comparison
rosiglitazone: PD, pharmacology
troglitazone: DT, drug therapy
troglitazone: PD, pharmacology
dexamethasone: CM, drug comparison
pioglitazone: DT, drug therapy
thalidomide: DT, drug therapy
n (2 benzoylphenyl) o [2 (methyl 2 pyridinylamino)ethyl]tyrosine: PD, pharmacology
15 deoxy delta12,14 prostaglandin J2: PD, pharmacology
nonsteroid antiinflammatory agent: CB, drug combination
nonsteroid antiinflammatory agent: DT, drug therapy
nonsteroid antiinflammatory agent: PD, pharmacology
sulindac sulfide: CB, drug combination
sulindac sulfide: PD, pharmacology
nimesulide: PD, pharmacology
unclassified drug

CAS REGISTRY NO.: (**ciglitazone**) **74772-77-3**; (farglitazar) 196808-45-4, 274687-78-4; (gw 501516) 317318-70-0; (**rosiglitazone**) **122320-73-4**, **155141-29-0**; (**troglitazone**) **97322-87-7**; (dexamethasone) 50-02-2; (**pioglitazone**) **105355-27-9**, **111025-46-8**; (thalidomide) 50-35-1; (n (2 benzoylphenyl) o [2 (methyl 2 pyridinylamino)ethyl]tyrosine) 196808-24-9; (15 deoxy delta12,14 prostaglandin J2) 87893-55-8; (sulindac sulfide) 49627-27-2; (nimesulide) 51803-78-2

CHEMICAL NAME: Gi 262570; Gw 9578; Gw 2331; Gw 501516

L148 ANSWER 39 OF 56 EMBASE

ACCESSION NUMBER: 2004300703 EMBASE

TITLE: Recent advances in understanding the pathogenesis of polycystic kidney disease: Therapeutic implications.

AUTHOR: Cowley Jr. B.D.

CORPORATE SOURCE: Prof. B.D. Cowley Jr., Nephrology/WP2250, Univ. of OK Health Sciences Center, 920 Stanton L. Young Blvd, Oklahoma City, OK 73104, United States. Ben-Cowley@ouhsc.edu

SOURCE: Drugs, (2004) Vol. 64, No. 12, pp. 1285-1294. .
Refs: 94
ISSN: 0012-6667 CODEN: DRUGAY

COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040805
Last Updated on STN: 20040805

ABSTRACT: Hereditary polycystic kidney disease (PKD) is a common cause of renal failure. Increasing knowledge is available regarding mechanisms of cyst development and progression, and renal functional deterioration in PKD. On the basis of this information and theories regarding the pathophysiology of these processes, studies to alter progression and potentially treat PKD have been reported. Cyst development and progression requires epithelial cell proliferation, transepithelial fluid secretion and extracellular matrix remodelling. Several interventions designed to inhibit cell proliferation or alter fluid secretion modify the progression of PKD in selected animal models. Renal functional deterioration appears to involve interstitial inflammation and fibrosis, and tubular apoptosis. Glucocorticoids with anti-inflammatory and antifibrotic properties slow the progression of **cystic** disease and renal functional deterioration in animal models of PKD. Other interventions, such as dietary modification and angiotensin antagonism, shown to be of benefit in non-PKD models of slowly progressive renal disease, are also of benefit in animal models of PKD. Caution should be used in extrapolating interventional studies in one animal model to another model and certainly to human disease, since examples exist in which treatments in one model of PKD have different effects in another model. Nonetheless, early attempts to determine whether potential treatments are tolerated and of potential benefit in patients with PKD are beginning to appear. Ultimately, treatment of PKD may involve efforts to identify patients at greatest risk for disease progression, thus allowing targeted therapy, use of surrogate markers for disease progression to assist assessment of therapeutic efficacy, and combination therapy to retard disease progression and renal functional deterioration in this common hereditary cause of chronic renal failure.

CONTROLLED TERM: Medical Descriptors:
*kidney polycystic disease: DT, drug therapy
*kidney polycystic disease: ET, etiology
pathogenesis
kidney failure: CO, complication
kidney function
disease course
epithelium cell
cell proliferation
cell secretion
extracellular matrix
fibrosing alveolitis: CO, complication
inflammation: CO, complication
apoptosis
protein restriction
disease marker
gene mutation
allele
protein expression
protein function
kidney dysfunction: PC, prevention
linseed

kidney disease: CO, complication
kidney disease: DT, drug therapy
nephrectomy
Heymann nephritis
smoking cessation
acidosis: DT, drug therapy
side effect: SI, side effect
human
nonhuman
clinical trial
article
Drug Descriptors:
glucocorticoid: DT, drug therapy
glucocorticoid: PD, pharmacology
polycystin 1: EC, endogenous compound
monocyte chemotactic protein: EC, endogenous compound
osteopontin: EC, endogenous compound
antiinflammatory agent: CB, drug combination
antifibrotic agent: CB, drug combination
epidermal growth factor receptor: DT, drug therapy
protein tyrosine kinase inhibitor: DT, drug therapy
antisense oligonucleotide: AE, adverse drug reaction
antisense oligonucleotide: CT, clinical trial
antisense oligonucleotide: DT, drug therapy
antisense oligonucleotide: PD, pharmacology
hydroxymethylglutaryl coenzyme A reductase inhibitor: CB, drug combination
hydroxymethylglutaryl coenzyme A reductase inhibitor: DT, drug therapy
hydroxymethylglutaryl coenzyme A reductase inhibitor: PD, pharmacology
vasopressin V2 receptor: EC, endogenous compound
hormone receptor blocking agent: DT, drug therapy
soybean protein
flaxseed extract: PD, pharmacology
plant extract: PD, pharmacology
dipeptidyl carboxypeptidase inhibitor: CB, drug combination
dipeptidyl carboxypeptidase inhibitor: DT, drug therapy
dipeptidyl carboxypeptidase inhibitor: PD, pharmacology
antioxidant
angiotensin receptor antagonist: CB, drug combination
angiotensin receptor antagonist: DT, drug therapy
mycophenolic acid 2 morpholinoethyl ester: CB, drug combination
mycophenolic acid 2 morpholinoethyl ester: DT, drug therapy
paclitaxel: DT, drug therapy
paclitaxel: TO, drug toxicity
bicarbonate: DT, drug therapy
methylprednisolone: DT, drug therapy
ammonium chloride: DT, drug therapy
alkali: DT, drug therapy
alkali: TO, drug toxicity
potassium bicarbonate: DT, drug therapy
citrate potassium: DT, drug therapy
mevinolin: DT, drug therapy
probucol: DT, drug therapy
pioglitazone: DT, drug therapy
unclassified drug

CAS REGISTRY NO.: (osteopontin) 106441-73-0; (soybean protein) 9010-10-0; (mycophenolic acid 2 morpholinoethyl ester) 116680-01-4,

128794-94-5; (paclitaxel) 33069-62-4; (bicarbonate) 144-55-8, 71-52-3; (methylprednisolone) 6923-42-8, 83-43-2; (ammonium chloride) 12125-02-9; (potassium bicarbonate) 298-14-6; (citrate potassium) 3609-96-9, 7778-49-6, 866-83-1, 866-84-2; (mevinolin) 75330-75-5; (probucol) 23288-49-5; **(pioglitazone) 105355-27-9, 111025-46-8**

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ACCESSION NUMBER: 2005005900 EMBASE
TITLE: Of herbs and vitamins.
AUTHOR: Saeed M.
CORPORATE SOURCE: M. Saeed, Dept. of Biol. and Biomed. Sciences, Aga Khan University, Karachi, Pakistan
SOURCE: Journal of the Pakistan Medical Association, (2004) Vol. 54, No. 11, pp. 592-594. .
ISSN: 0030-9982 CODEN: JPKMAK
COUNTRY: Pakistan
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 002 Physiology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 20050113
Last Updated on STN: 20050113
CONTROLLED TERM: Medical Descriptors:
*herbal medicine
*vitamin supplementation
diabetes mellitus: TH, therapy
fruit juice
tomato
malaria falciparum: DT, drug therapy
hematologic malignancy: DT, drug therapy
congestive heart failure: DT, drug therapy
rheumatic disease: DT, drug therapy
cystic fibrosis: DT, drug therapy
cystic fibrosis: ET, etiology
treatment outcome
survival rate
practice guideline
ST segment elevation
heart infarction: SU, surgery
coronary artery bypass graft
cardiovascular disease
cardiovascular risk
common cold
low drug dose
natural killer cell
cancer inhibition
antineoplastic activity
chickenpox: DT, drug therapy
chickenpox: EP, epidemiology
chickenpox: ET, etiology
chickenpox: PC, prevention
vaccination
drug indication
febrile convulsion: SI, side effect

risk factor
muscle contraction
exercise
muscle fatigue
sarcoplasmic reticulum
action potential
membrane depolarization
acidosis
chloride transport
cell membrane permeability
sodium current
human
nonhuman
clinical trial
review
Drug Descriptors:
quinine: DT, drug therapy
artemisinin: DT, drug therapy
vincristine: DT, drug therapy
digitalis: DT, drug therapy
salicylic acid derivative: DT, drug therapy
hemoglobin A1c: EC, endogenous compound
transmembrane conductance regulator: EC, endogenous compound
curcumin: DT, drug therapy
curcumin: PD, pharmacology
curcumin: PO, oral drug administration
Curcuma longa extract: DT, drug therapy
Curcuma longa extract: PD, pharmacology
Curcuma longa extract: PO, oral drug administration
alpha tocopherol: CT, clinical trial
alpha tocopherol: CB, drug combination
alpha tocopherol: DT, drug therapy
alpha tocopherol: PD, pharmacology
palm oil
tamoxifen: CT, clinical trial
tamoxifen: CB, drug combination
tamoxifen: DT, drug therapy
troglitazone: PD, pharmacology
chickenpox vaccine: DT, drug therapy
measles mumps rubella vaccine: AE, adverse drug reaction

CAS REGISTRY NO.: (quinine) 130-89-2, 130-95-0, 14358-44-2, 549-48-4, 549-49-5, 60-93-5, 7549-43-1; (artemisinin) 63968-64-9; (vincristine) 57-22-7; (digitalis) 8031-42-3, 8053-83-6; (hemoglobin A1c) 62572-11-6; (curcumin) 458-37-7; (alpha tocopherol) 1406-18-4, 1406-70-8, 52225-20-4, 58-95-7, 59-02-9; (palm oil) 8002-75-3; (tamoxifen) 10540-29-1; (**troglitazone**) **97322-87-7**

L148 ANSWER 41 OF 56 EMBASE

ACCESSION NUMBER: 2005075920 EMBASE
TITLE: Clinical importance of **cystic** fibrosis-related diabetes.
AUTHOR: Brennan A.L.; Geddes D.M.; Gyi K.M.; Baker E.H.
CORPORATE SOURCE: A.L. Brennan, Department of Physiological Medicine, St. George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, United Kingdom. albrenna@sghms.ac.uk
SOURCE: Journal of Cystic Fibrosis, (2004) Vol. 3, No. 4, pp. 209-222. .

Refs: 97
ISSN: 1569-1993 CODEN: JCFOAC
PUBLISHER IDENT.: S 1569-1993(04)00169-9
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
015 Chest Diseases, Thoracic Surgery and Tuberculosis
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050303
Last Updated on STN: 20050303

ABSTRACT: The prevalence of **cystic** fibrosis-related diabetes (CFRD) and glucose intolerance (IGT) has risen dramatically over the past 20 years as survival has increased for people with **cystic** fibrosis (CF). Diabetes is primarily caused by pancreatic damage, which reduces insulin secretion, but glucose tolerance is also modified by factors that alter insulin resistance, such as intercurrent illness and infection. CFRD not only causes the symptoms and micro and macrovascular complications seen in type 1 and type 2 diabetes in the general population, but also is associated with accelerated pulmonary decline and increased mortality. Pulmonary effects are seen some years before the diagnosis of CFRD, implying that impaired glucose tolerance may be detrimental. Current practice is to screen for changes in glucose tolerance by regular measurement of fasting blood glucose, by oral glucose tolerance test or a combination of these approaches with symptom review and measurement of HbA(1C). Treatment is clearly indicated for those with CFRD and fasting hyperglycaemia to control symptoms and reduce complications. As nutrition is critical in people with CF to maintain body mass and lung function, blood glucose should be controlled in CFRD by adjusting insulin doses to the requirements of adequate food intake and not by calorie restriction. It is less clear whether blood glucose control will have clinical benefits in the management of patients with CFRD without fasting hyperglycaemia or with impaired glucose tolerance and further studies are required to establish the best treatment for this patient group.

CONTROLLED TERM: Medical Descriptors:
***cystic fibrosis: DT, drug therapy**
*diabetes mellitus: DI, diagnosis
*diabetes mellitus: DT, drug therapy
*diabetes mellitus: TH, therapy
prevalence
glucose intolerance
disease association
survival
pancreas injury
insulin release
insulin resistance
infection
microangiopathy: CO, complication
vascular disease: CO, complication
insulin dependent diabetes mellitus
non insulin dependent diabetes mellitus
lung function
mortality
clinical practice
screening test
glucose blood level

oral glucose tolerance test
diagnostic approach route
treatment indication
hyperglycemia
nutrition
body mass
food intake
drug dose regimen
caloric restriction
blood glucose monitoring
abdominal pain: SI, side effect
gastrointestinal symptom: SI, side effect
nausea: SI, side effect
diarrhea: SI, side effect
drug mechanism
drug efficacy
drug half life
human
clinical trial
review
Drug Descriptors:
insulin: CM, drug comparison
insulin: DO, drug dose
insulin: DT, drug therapy
insulin: EC, endogenous compound
glucose: EC, endogenous compound
repaglinide: CT, clinical trial
repaglinide: DT, drug therapy
repaglinide: PK, pharmacokinetics
repaglinide: PO, oral drug administration
metformin: AE, adverse drug reaction
metformin: DT, drug therapy
2,4 thiazolidinedione derivative: PD, pharmacology
antibiotic agent: PO, oral drug administration
mucolytic agent: DT, drug therapy
vitamin: DT, drug therapy
sulfonylurea derivative: CM, drug comparison
sulfonylurea derivative: DT, drug therapy
sulfonylurea derivative: PD, pharmacology
glibenclamide: CM, drug comparison
glibenclamide: DT, drug therapy
CAS REGISTRY NO.: (insulin) 9004-10-8; (glucose) 50-99-7, 84778-64-3; (repaglinide) 135062-02-1; (metformin) 1115-70-4, 657-24-9; (glibenclamide) 10238-21-8

L148 ANSWER 42 OF 56 EMBASE
ACCESSION NUMBER: 2005042593 EMBASE
TITLE: Insulins and oral hypoglycemic medications.
AUTHOR: Hale D.E.; Kiess W.
CORPORATE SOURCE: Dr. D.E. Hale, Department of Pediatrics, 7703 Floyd Curl Drive, San Antonio, TX 78229, United States. hale@uthscsa.edu
SOURCE: Pediatric Endocrinology Reviews, (2004) Vol. 2, No. SUPPL. 1, pp. 153-162. .
Refs: 72
ISSN: 1565-4753
COUNTRY: Israel
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology

007 Pediatrics and Pediatric Surgery
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050210
Last Updated on STN: 20050210

ABSTRACT: The management of childhood diabetes is rapidly evolving, reflecting both the recognition of new types of diabetes in pediatrics and the availability of new insulins. Over the past two decades there have been increasing numbers of children affected by type 2 diabetes, maturity onset diabetes of youth (MODY), and medical diabetes secondary to medication usage (e.g. prednisone) or disease process (e.g., **cystic** fibrosis). These forms of diabetes require familiarity with medications other than insulin and an understanding of appropriate treatment strategies. Simultaneously, after years of little change, there has been the relatively rapid introduction of new insulins (e.g., lispro, aspart, glargine) and more sophisticated means of insulin delivery (e.g., pumps, pens, inhalers). Taken as a whole, these trends present a challenge to the pediatric diabetes specialist. In this article, the medications that are now frequently used in diabetes treatment are reviewed, including the indications for use, the usual dose, dose adjustment strategies, common side effects and anticipated outcomes. The diabetes literature on the new insulins and diabetes medications is reviewed, with an emphasis on the limited pediatric data. The goal is to familiarize the practicing pediatric diabetes specialist with these medications and their usage.

CONTROLLED TERM: Medical Descriptors:
*diabetes mellitus: DT, drug therapy
*insulin treatment
childhood disease: DT, drug therapy
insulin dependent diabetes mellitus: DT, drug therapy
non insulin dependent diabetes mellitus: DT, drug therapy
juvenile diabetes mellitus: DT, drug therapy
maturity onset diabetes mellitus: DT, drug therapy
drug indication
drug dose regimen
hypoglycemia: SI, side effect
hyperglycemia: DI, diagnosis
hyperglycemia: ET, etiology
lipoatrophy: SI, side effect
lipohypertrophy: SI, side effect
edema: SI, side effect
acanthosis nigricans: SI, side effect
injection site reaction: SI, side effect
insulin pump
drug absorption
respiratory tract disease: SI, side effect
gastrointestinal symptom: SI, side effect
nausea: SI, side effect
abdominal pain: SI, side effect
vomiting: SI, side effect
diarrhea: SI, side effect
musculoskeletal disease: SI, side effect
myalgia: SI, side effect
arthralgia: SI, side effect
backache: SI, side effect
skin toxicity: SI, side effect
pruritus: SI, side effect
erythema: SI, side effect
urticaria: SI, side effect

cardiotoxicity: SI, side effect
lactic acidosis: SI, side effect
flatulence: SI, side effect
body weight disorder: SI, side effect
weight gain
fluid retention
side effect: SI, side effect
liver dysfunction: SI, side effect
abdominal discomfort: SI, side effect
abdominal cramp: SI, side effect
add on therapy
human
clinical trial
child
review
Drug Descriptors:
*antidiabetic agent: AE, adverse drug reaction
*antidiabetic agent: CT, clinical trial
*antidiabetic agent: CB, drug combination
*antidiabetic agent: DO, drug dose
*antidiabetic agent: DT, drug therapy
*antidiabetic agent: PD, pharmacology
*antidiabetic agent: IH, inhalational drug administration
*antidiabetic agent: IM, intramuscular drug administration
*antidiabetic agent: IV, intravenous drug administration
*antidiabetic agent: PO, oral drug administration
*insulin: AE, adverse drug reaction
*insulin: CT, clinical trial
*insulin: CB, drug combination
*insulin: DO, drug dose
*insulin: DT, drug therapy
*insulin: PK, pharmacokinetics
*insulin: PD, pharmacology
*insulin: IH, inhalational drug administration
*insulin: IM, intramuscular drug administration
*insulin: IV, intravenous drug administration
*oral antidiabetic agent: CT, clinical trial
*oral antidiabetic agent: CB, drug combination
*oral antidiabetic agent: DO, drug dose
*oral antidiabetic agent: DT, drug therapy
*oral antidiabetic agent: PD, pharmacology
*oral antidiabetic agent: PO, oral drug administration
*insulin secretagogue: AE, adverse drug reaction
*insulin secretagogue: CT, clinical trial
*insulin secretagogue: CB, drug combination
*insulin secretagogue: DO, drug dose
*insulin secretagogue: DT, drug therapy
*insulin secretagogue: PK, pharmacokinetics
*insulin secretagogue: PD, pharmacology
*insulin secretagogue: PO, oral drug administration
*insulin sensitizing agent: AE, adverse drug reaction
*insulin sensitizing agent: CT, clinical trial
*insulin sensitizing agent: DO, drug dose
*insulin sensitizing agent: DT, drug therapy
*insulin sensitizing agent: PD, pharmacology
*glucose uptake blocker: AE, adverse drug reaction
*glucose uptake blocker: DT, drug therapy
*glucose uptake blocker: PD, pharmacology
insulin antibody
insulin[B28 lysine B29 proline]: DT, drug therapy

insulin[B28 lysine B29 proline]: PK, pharmacokinetics
insulin[B28 lysine B29 proline]: PD, pharmacology
insulin aspart: DT, drug therapy
insulin aspart: PK, pharmacokinetics
insulin aspart: PD, pharmacology
insulin zinc suspension: DT, drug therapy
insulin zinc suspension: PK, pharmacokinetics
insulin zinc suspension: PD, pharmacology
insulin detemir: DT, drug therapy
insulin detemir: PK, pharmacokinetics
insulin detemir: PD, pharmacology
isophane insulin: DT, drug therapy
isophane insulin: PK, pharmacokinetics
isophane insulin: PD, pharmacology
insulin glargine: DT, drug therapy
insulin glargine: PK, pharmacokinetics
insulin glargine: PD, pharmacology
sulfonylurea derivative: AE, adverse drug reaction
sulfonylurea derivative: DO, drug dose
sulfonylurea derivative: DT, drug therapy
sulfonylurea derivative: PD, pharmacology
sulfonylurea derivative: PO, oral drug administration
glibenclamide: AE, adverse drug reaction
glibenclamide: CT, clinical trial

CONTROLLED TERM: Drug Descriptors:
glibenclamide: CB, drug combination
glibenclamide: CM, drug comparison
glibenclamide: DO, drug dose
glibenclamide: DT, drug therapy
glibenclamide: PD, pharmacology
glibenclamide: PO, oral drug administration
glipizide: AE, adverse drug reaction
glipizide: DO, drug dose
glipizide: DT, drug therapy
glipizide: PD, pharmacology
glipizide: PO, oral drug administration
glimepiride: AE, adverse drug reaction
glimepiride: CT, clinical trial
glimepiride: CB, drug combination
glimepiride: DO, drug dose
glimepiride: DT, drug therapy
glimepiride: PD, pharmacology
glimepiride: PO, oral drug administration
meglitinide: DT, drug therapy
meglitinide: PD, pharmacology
meglitinide: PO, oral drug administration
metformin: AE, adverse drug reaction
metformin: CT, clinical trial
metformin: CB, drug combination
metformin: CM, drug comparison
metformin: DO, drug dose
metformin: DT, drug therapy
metformin: PD, pharmacology
metformin: PO, oral drug administration
nateglinide: AE, adverse drug reaction
nateglinide: CT, clinical trial
nateglinide: CB, drug combination
nateglinide: DO, drug dose
nateglinide: DT, drug therapy

nateglinide: PD, pharmacology
nateglinide: PO, oral drug administration
repaglinide: AE, adverse drug reaction
repaglinide: CT, clinical trial
repaglinide: DO, drug dose
repaglinide: DT, drug therapy
repaglinide: PD, pharmacology
repaglinide: PO, oral drug administration
2,4 thiazolidinedione derivative: AE, adverse drug reaction
2,4 thiazolidinedione derivative: CT, clinical trial
2,4 thiazolidinedione derivative: DO, drug dose
2,4 thiazolidinedione derivative: DT, drug therapy
2,4 thiazolidinedione derivative: PD, pharmacology
2,4 thiazolidinedione derivative: PO, oral drug administration
rosiglitazone: AE, adverse drug reaction
rosiglitazone: CT, clinical trial
rosiglitazone: DT, drug therapy
rosiglitazone: PD, pharmacology
acarbose: AE, adverse drug reaction
acarbose: CT, clinical trial
acarbose: CB, drug combination
acarbose: DT, drug therapy
acarbose: PD, pharmacology
tetrahydrolipstatin: DT, drug therapy
tetrahydrolipstatin: PD, pharmacology
unclassified drug

CAS REGISTRY NO.: (insulin) 9004-10-8; (insulin[B28 lysine B29 proline]) 133107-64-9; (insulin aspart) 116094-23-6; (insulin zinc suspension) 8049-62-5; (insulin detemir) 169148-63-4, 201305-44-4, 270588-25-5; (isophane insulin) 9004-17-5; (insulin glargine) 160337-95-1; (glibenclamide) 10238-21-8; (glipizide) 29094-61-9; (glimepiride) 93479-97-1; (meglitinide) 54870-28-9; (metformin) 1115-70-4, 657-24-9; (nateglinide) 105746-37-0, 105816-04-4, 105816-06-6; (repaglinide) 135062-02-1; (**rosiglitazone**) **122320-73-4, 155141-29-0**; (acarbose) 56180-94-0; (tetrahydrolipstatin) 96829-58-2

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ACCESSION NUMBER: 2004282801 EMBASE

TITLE: **Troglitazone** inhibits the progression of chronic pancreatitis and the profibrogenic activity of pancreatic stellate cells via a PPARγ- independent mechanism.

AUTHOR: Shimizu K.; Shiratori K.; Kobayashi M.; Kawamata H.

CORPORATE SOURCE: Dr. K. Shimizu, Dept. of Clin. Lab./Gastroenterol., Tokyo Women's Medical University, School of Medicine, 8-1, Kawada-cho, Shinjuku-ku Tokyo 162-8666, Japan. kyoko@ige.twmu.ac.jp

SOURCE: Pancreas, (2004) Vol. 29, No. 1, pp. 67-74. .
Refs: 38
ISSN: 0885-3177 CODEN: PANCE4

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 006 Internal Medicine
030 Pharmacology
037 Drug Literature Index

048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040722
Last Updated on STN: 20040722

ABSTRACT: We have previously reported that **troglitazone** inhibits proinflammatory cytokine production in chronic pancreatitis. In the present study, we show that **troglitazone** prevents the progression of chronic pancreatitis by inhibiting the proliferation of pancreatic stellate cells (PSCs) via a PPARγ-independent mechanism. WBN/Kob rats with spontaneous chronic pancreatitis were fed **troglitazone**-containing rat chow for 3 or 6 months. Pancreatic fibrosis and expression of α-SMA were markedly attenuated by **troglitazone.** Rat PSCs expressed a higher level of PPARγ1 mRNA than of PPARγ2 mRNA. PSCs were transiently cotransfected with a dominant negative mutant PPARγ1 and a PPAR-driven reporter gene. **Troglitazone** increased reporter activity and the mutant receptor abrogated wild-type receptor activity in a dose-dependent manner. **Troglitazone** inhibited cell proliferation by blocking cell-cycle progression beyond the G(1) phase. These effects were observed in mutant receptor-transfected cells as well as cells transfected with the control vector. The effect of **troglitazone** on α1(I) procollagen mRNA and MCP-1 mRNA was unaffected by inhibition of endogenous PPARγ1 receptor activity. These results suggest that **troglitazone** may serve as novel therapeutic agent for the treatment of chronic pancreatitis. The antifibrotic effect of **troglitazone** appears to be mediated, in part, via a PPARγ-independent mechanism.

CONTROLLED TERM: Medical Descriptors:
*chronic pancreatitis: DT, drug therapy
*drug activity
*stellate cell
drug mechanism
antiinflammatory activity
cytokine production
cystic fibrosis
antigen expression
genetic transfection
wild type
cell proliferation
gene activity
reporter gene
cell cycle G1 phase
drug effect
nonhuman
male
rat
controlled study
animal cell
article
priority journal
Drug Descriptors:
***troglitazone: DT, drug therapy**
***troglitazone: PD, pharmacology**
*peroxisome proliferator activated receptor gamma: EC, endogenous compound
messenger RNA: EC, endogenous compound
alpha actin: EC, endogenous compound
procollagen: EC, endogenous compound
monocyte chemotactic protein 1: EC, endogenous compound
CAS REGISTRY NO.: (**troglitazone**) **97322-87-7**

COMPANY NAME: Sankyo (Japan)

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ACCESSION NUMBER: 2004231204 EMBASE
TITLE: Understanding **cystic**-fibrosis-related diabetes: Best thought of as insulin deficiency?.
AUTHOR: Dobson L.; Sheldon C.D.; Hattersley A.T.
CORPORATE SOURCE: Prof. A.T. Hattersley, Diabetes and Vascular Medicine, Peninsula Medical School, Barrack Road, Exeter EX2 5AX, United Kingdom. A.T.Hattersley@ex.ac.uk
SOURCE: Journal of the Royal Society of Medicine, Supplement, (2004) Vol. 97, No. 44, pp. 26-35. .
Refs: 78
ISSN: 0267-5331 CODEN: JRMSEW
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 003 Endocrinology
006 Internal Medicine
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 20040617
Last Updated on STN: 20040617
CONTROLLED TERM: Medical Descriptors:
***cystic fibrosis**
*diabetes mellitus: DT, drug therapy
*insulin deficiency
screening
diagnostic procedure
glucose blood level
glucose tolerance test
oral glucose tolerance test
glucose urine level
incidence
prevalence
mortality
morbidity
pathophysiology
pancreas islet beta cell
pancreas islet alpha cell
cell function
insulin resistance
clearance
diet
glucose transport
lactic acidosis: SI, side effect
hypoxia: SI, side effect
diarrhea: SI, side effect
anorexia: SI, side effect
abdominal discomfort: SI, side effect
human
clinical trial
conference paper
Drug Descriptors:
hemoglobin A1c: EC, endogenous compound
insulin: DT, drug therapy
insulin: EC, endogenous compound
antidiabetic agent: DT, drug therapy
antidiabetic agent: PO, oral drug administration

tolbutamide: DT, drug therapy
tolbutamide: IV, intravenous drug administration
glipizide: CT, clinical trial
glipizide: DT, drug therapy
glucose: IV, intravenous drug administration
glibenclamide: DT, drug therapy
biguanide: AE, adverse drug reaction
biguanide: DT, drug therapy
metformin: AE, adverse drug reaction
metformin: DT, drug therapy
acarbose: AE, adverse drug reaction
acarbose: DT, drug therapy
2,4 thiazolidinedione derivative: DT, drug therapy
repaglinide: AE, adverse drug reaction
repaglinide: CM, drug comparison
repaglinide: DT, drug therapy
repaglinide: PD, pharmacology

CAS REGISTRY NO.: (hemoglobin A1c) 62572-11-6; (insulin) 9004-10-8; (tolbutamide) 473-41-6, 64-77-7; (glipizide) 29094-61-9; (glucose) 50-99-7, 84778-64-3; (glibenclamide) 10238-21-8; (biguanide) 56-03-1; (metformin) 1115-70-4, 657-24-9; (acarbose) 56180-94-0; (repaglinide) 135062-02-1

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ACCESSION NUMBER: 2004019358 EMBASE
TITLE: IDdb new focus.
SOURCE: Current Drug Discovery, (2003) No. DEC., pp. 12. .
ISSN: 1472-7463 CODEN: CDDUAI
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 006 Internal Medicine
008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
ENTRY DATE: Entered STN: 20040122
Last Updated on STN: 20040122
CONTROLLED TERM: Medical Descriptors:
*drug research
neuropathic pain: DT, drug therapy
rheumatoid arthritis: DT, drug therapy
cystic fibrosis: DT, drug therapy
retina detachment: DT, drug therapy
retina edema: DT, drug therapy
allergic rhinitis: DT, drug therapy
diabetes mellitus: DT, drug therapy
drug mechanism
liver toxicity: SI, side effect
structure activity relation
drug formulation
drug efficacy
low drug dose
controlled release formulation
cardiovascular disease: DT, drug therapy
thrombosis: DT, drug therapy
drug metabolism
pulmonary hypertension: DT, drug therapy

drug screening
drug industry
biotechnology
human
clinical trial
note
Drug Descriptors:
purinergic receptor blocking agent: CT, clinical trial
purinergic receptor blocking agent: DT, drug therapy
purinergic receptor blocking agent: PD, pharmacology
purinergic receptor blocking agent: NA, intranasal drug administration
ins 48506: DT, drug therapy
ins 48506: PD, pharmacology
azd 9056: CT, clinical trial
azd 9056: DT, drug therapy
azd 9056: PD, pharmacology
isis 13920: DT, drug therapy
isis 13920: PD, pharmacology
ins 37217: CT, clinical trial
ins 37217: DT, drug therapy
ins 37217: PD, pharmacology
ins 37217: NA, intranasal drug administration
antisense oligonucleotide
peroxisome proliferator activated receptor agonist: AE, adverse drug reaction
peroxisome proliferator activated receptor agonist: CT, clinical trial
peroxisome proliferator activated receptor agonist: DT, drug therapy
peroxisome proliferator activated receptor agonist: PD, pharmacology
rosiglitazone: AE, adverse drug reaction
rosiglitazone: CT, clinical trial
rosiglitazone: DT, drug therapy
rosiglitazone: PD, pharmacology
pioglitazone: AE, adverse drug reaction
pioglitazone: CT, clinical trial
pioglitazone: DT, drug therapy
pioglitazone: PD, pharmacology
troglitazone: AE, adverse drug reaction
troglitazone: CT, clinical trial
troglitazone: DT, drug therapy
troglitazone: PD, pharmacology
insulin sensitizing agent: AE, adverse drug reaction
insulin sensitizing agent: CT, clinical trial
insulin sensitizing agent: AN, drug analysis
insulin sensitizing agent: DT, drug therapy
insulin sensitizing agent: PD, pharmacology
mbx 2044: CT, clinical trial
mbx 2044: DT, drug therapy
mbx 2044: PD, pharmacology
mbx 102: CT, clinical trial
mbx 102: AN, drug analysis
mbx 102: DT, drug therapy
mbx 102: PD, pharmacology
mbx 675: CT, clinical trial
mbx 675: DT, drug therapy
mbx 675: PD, pharmacology
oxycodone: CT, clinical trial

oxycodone: CB, drug combination
oxycodone: DT, drug therapy
oxycodone: PR, pharmaceutics
oxycodone: PD, pharmacology
oxycodone: PO, oral drug administration
long acting drug: CT, clinical trial
long acting drug: CB, drug combination
long acting drug: DT, drug therapy
long acting drug: PR, pharmaceutics
long acting drug: PD, pharmacology
long acting drug: PO, oral drug administration
morphine derivative: CT, clinical trial
morphine derivative: PR, pharmaceutics
morphine derivative: PD, pharmacology
morphine derivative: IV, intravenous drug administration
morphine derivative: PO, oral drug administration
pti 555: CT, clinical trial
pti 555: PR, pharmaceutics
pti 555: PD, pharmacology
pti 555: IV, intravenous drug administration
pti 555: PO, oral drug administration
pti 501: CT, clinical trial
pti 501: PR, pharmaceutics
pti 501: PD, pharmacology
pti 501: IV, intravenous drug administration
pti 501: PO, oral drug administration
naltrexone: CT, clinical trial
naltrexone: CB, drug combination
naltrexone: DO, drug dose
naltrexone: PR, pharmaceutics
naltrexone: PD, pharmacology
naltrexone: IV, intravenous drug administration
naltrexone: PO, oral drug administration
hydroxymethylglutaryl coenzyme A reductase inhibitor: DT, drug therapy
hydroxymethylglutaryl coenzyme A reductase inhibitor: PD, pharmacology
ncx 6550: DT, drug therapy
ncx 6550: PD, pharmacology
ncx 6554: DT, drug therapy
ncx 6554: PD, pharmacology
ncx 5022: DT, drug therapy
ncx 5022: PD, pharmacology
malonyl coenzyme A: EC, endogenous compound
enzyme inhibitor: CT, clinical trial

CONTROLLED TERM: Drug Descriptors:
enzyme inhibitor: PK, pharmacokinetics
enzyme inhibitor: PD, pharmacology
cbi 300864: CT, clinical trial
cbi 300864: PK, pharmacokinetics
cbi 300864: PD, pharmacology
antineoplastic agent: DV, drug development
antineoplastic agent: PD, pharmacology
iloprost: DT, drug therapy
unindexed drug
unclassified drug
oxytrex
remoxy

CAS REGISTRY NO.: **(rosiglitazone) 122320-73-4, 155141-29-0; (pioglitazone)**

105355-27-9, **111025-46-8**; (**troglitazone**) **97322-87-7**; (oxycodone) 124-90-3, 76-42-6; (naltrexone) 16590-41-3, 16676-29-2; (malonyl coenzyme A) 524-14-1; (iloprost) 78919-13-8, 82889-99-4

CHEMICAL NAME: (1) Azd 9056; (2) Isis 13920; **(3) Avandia**; **(4) Actos**; **(5) Rezulin**; (6) Mbx 2044; (7) Mbx 102; (8) Mbx 675; (9) Pti 555; (10) Pti 501; (11) Oxytrex; (12) Ncx 6550; (13) Ncx 6554; (14) Ncx 5022; (15) Remoxy; (16) Cbi 300864; Ins 48506; Ins 37217

COMPANY NAME: (1) Astra Zeneca; (2) Abbott; (3) Glaxo SmithKline; (4) Takeda; (5) Sankyo (Japan); (8) Metabolex; (14) Nicox; (15) Pain Therapeutics; (16) Chugai; Cambridge Research; Phenomix; Plexxikon; Schering

L148 ANSWER 46 OF 56 EMBASE

ACCESSION NUMBER: 2003278657 EMBASE

TITLE: Opinion and evidence for treatments in endocrine disorders.

SOURCE: Treatments in Endocrinology, (2002) Vol. 1, No. 2, pp. 131-141. .
ISSN: 1175-6349 CODEN: TERNAN

COUNTRY: New Zealand

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 003 Endocrinology
010 Obstetrics and Gynecology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20030731
Last Updated on STN: 20030731

ABSTRACT: New treatments and treatment protocols for endocrine disorders are evolving rapidly, and research and development activity in the endocrinology field is high. Optimal therapy remains contentious in some areas. To help you keep up-to-date with the latest advances worldwide on all aspects of drug therapy and management of endocrine disorders, this section of thejournal brings you information selected from the rapid drug news alerting service Inpharma Weekly. Each issue contains easy-to-read summaries of the most important research and development news, clinical studies, treatment guidelines, pharmacoeconomic and adverse drug reaction news, and expert opinion pieces published in the world's top endocrinology journals.

CONTROLLED TERM: Medical Descriptors:
*endocrine disease: DM, disease management
*endocrine disease: DT, drug therapy
practice guideline
drug monitoring
non insulin dependent diabetes mellitus: DM, disease management
non insulin dependent diabetes mellitus: DT, drug therapy
abdominal pain: SI, side effect
nausea: SI, side effect
vomiting: SI, side effect
headache: SI, side effect
breast cancer: DT, drug therapy
breast cancer: PC, prevention
breast cancer: SI, side effect
hypertension: DT, drug therapy

Alzheimer disease: DT, drug therapy
Alzheimer disease: PC, prevention
cardiovascular disease: DT, drug therapy
cardiovascular disease: PC, prevention
adrenal insufficiency: DT, drug therapy
vertebra fracture: DT, drug therapy
vertebra fracture: PC, prevention
obesity: DT, drug therapy
hypercholesterolemia: DT, drug therapy
cystic fibrosis: DT, drug therapy
pancreatitis: SI, side effect
heart infarction: SI, side effect
stroke: SI, side effect
sudden death
side effect: SI, side effect
heart arrhythmia: SI, side effect
seizure: SI, side effect
psychosis: SI, side effect
postmenopause osteoporosis: DT, drug therapy
postmenopause osteoporosis: PC, prevention
human
clinical trial
randomized controlled trial
controlled study
review
priority journal
Drug Descriptors:
metformin: CT, clinical trial
metformin: DT, drug therapy
metformin: PE, pharmacoeconomics
estrogen: AE, adverse drug reaction
estrogen: CB, drug combination
estrogen: DT, drug therapy
gestagen: AE, adverse drug reaction
gestagen: CB, drug combination
gestagen: CM, drug comparison
gestagen: DT, drug therapy
gestagen: PE, pharmacoeconomics
dipeptidyl carboxypeptidase inhibitor: DT, drug therapy
angiotensin receptor antagonist: DT, drug therapy
diuretic agent: DT, drug therapy
beta adrenergic receptor blocking agent: DT, drug therapy
alpha adrenergic receptor blocking agent: DT, drug therapy
estradiol: DT, drug therapy
estradiol: PO, oral drug administration
corticosteroid: AE, adverse drug reaction
dexamethasone: DT, drug therapy
prednisone: DT, drug therapy
fludrocortisone: DT, drug therapy
fludrocortisone: PO, oral drug administration
hydrocortisone: DT, drug therapy
methylprednisolone: DT, drug therapy
raloxifene: CT, clinical trial
raloxifene: CM, drug comparison
raloxifene: DT, drug therapy
raloxifene: PE, pharmacoeconomics
raloxifene: PD, pharmacology
tetrahydrolipstatin: DT, drug therapy
human growth hormone: DT, drug therapy
human growth hormone: SC, subcutaneous drug administration

rosiglitazone: DT, drug therapy
alendronic acid: AE, adverse drug reaction
Ephedra extract: AE, adverse drug reaction
Ephedra extract: CB, drug combination
caffeine: AE, adverse drug reaction
caffeine: CB, drug combination
antidiabetic agent: DT, drug therapy
antidiabetic agent: PO, oral drug administration
sulfonylurea derivative: DT, drug therapy
sulfonylurea derivative: PO, oral drug administration
biguanide derivative: DT, drug therapy
biguanide derivative: PO, oral drug administration
alpha glucosidase inhibitor: DT, drug therapy
alpha glucosidase inhibitor: PO, oral drug administration
nateglinide: DT, drug therapy
nateglinide: PO, oral drug administration
conjugated estrogen: CM, drug comparison
conjugated estrogen: DT, drug therapy
conjugated estrogen: PE, pharmacoeconomics
conjugated estrogen: PO, oral drug administration
oral contraceptive agent: AE, adverse drug reaction
oral contraceptive agent: PO, oral drug administration
unindexed drug

CAS REGISTRY NO.: (metformin) 1115-70-4, 657-24-9; (estradiol) 50-28-2; (dexamethasone) 50-02-2; (prednisone) 53-03-2; (fludrocortisone) 127-31-1; (hydrocortisone) 50-23-7; (methylprednisolone) 6923-42-8, 83-43-2; (raloxifene) 82640-04-8, 84449-90-1; (tetrahydrolipstatin) 96829-58-2; (human growth hormone) 12629-01-5; (**rosiglitazone**) **122320-73-4**, **155141-29-0**; (alendronic acid) 66376-36-1; (caffeine) 30388-07-9, 58-08-2; (nateglinide) 105746-37-0, 105816-04-4, 105816-06-6

L148 ANSWER 47 OF 56 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001212418 EMBASE
TITLE: Pharmacogenomics: Will it change the field of medicine?.
AUTHOR: Wieczorek S.J.; Tsongalis G.J.
CORPORATE SOURCE: G.J. Tsongalis, Department of Pathology Medicine, Hartford Hospital, 80 Seymour Street, Hartford, CT 06102, United States. gtsonga@harthosp.org
SOURCE: Clinica Chimica Acta, (2001) Vol. 308, No. 1-2, pp. 1-8. .
Refs: 55
ISSN: 0009-8981 CODEN: CCATAR
PUBLISHER IDENT.: S 0009-8981(01)00419-3
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 022 Human Genetics
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20010628
Last Updated on STN: 20010628

ABSTRACT: Pharmacogenomics has become increasingly important in healthcare, both from the standpoint of new drug development and primary care. Industry will benefit from the identification of new targets, screening of new therapeutic agents for adverse affects before clinical trials, and tailoring of therapeutic agents to individual patients. Physicians and patients will benefit since the medication and method of therapy can be tailored for the

maximum health effects. In the near future, genetic profiles of individual patients, via an electronic medical record, will be available to clinicians so that therapeutic strategies may be optimized from the time of initial therapy. As the Human Genome Project comes to an end, we must continue to gather information identifying SNPs and genes as well as clinical data to support the medical efficacy of such genetic profiling.

CONTROLLED TERM: Medical Descriptors:
*pharmacogenomics
drug response
drug metabolism
history of medicine
drug transport
cystic fibrosis
drug receptor binding
drug induced disease: SI, side effect
exercise
gastrointestinal disease
human
review
priority journal
Drug Descriptors:
cytochrome P450: EC, endogenous compound
cytochrome P450 3A: EC, endogenous compound
cytochrome P450 2D6: EC, endogenous compound
cytochrome P450 2C19: EC, endogenous compound
cytochrome P450 2C9: EC, endogenous compound
anticonvulsive agent
rifampicin
antifungal agent: IT, drug interaction
macrolide
mibefradil: AE, adverse drug reaction
mibefradil: IT, drug interaction
antihypertensive agent: AE, adverse drug reaction
antihypertensive agent: IT, drug interaction
simvastatin: AE, adverse drug reaction
simvastatin: IT, drug interaction
troglitazone: AE, adverse drug reaction
troglitazone: PD, pharmacology
cyclosporin
terfenadine
atorvastatin
fexofenadine
cisapride: IT, drug interaction
proteinase inhibitor: IT, drug interaction
calcium channel blocking agent: IT, drug interaction
digitalis glycoside
digoxin
cyclosporin A
carrier protein
drug receptor
isoprenaline
xanthine derivative: PD, pharmacology
salbutamol
formoterol

CAS REGISTRY NO.: (cytochrome P450) 9035-51-2; (rifampicin) 13292-46-1; (mibefradil) 116666-63-8; (simvastatin) 79902-63-9; (**troglitazone**) **97322-87-7**; (cyclosporin) 79217-60-0; (terfenadine) 50679-08-8; (atorvastatin) 134523-00-5, 134523-03-8; (fexofenadine) 138452-21-8;

(cisapride) 81098-60-4; (proteinase inhibitor) 37205-61-1; (digoxin) 20830-75-5, 57285-89-9; (cyclosporin A) 59865-13-3, 63798-73-2; (carrier protein) 80700-39-6; (isoprenaline) 299-95-6, 51-30-9, 6700-39-6, 7683-59-2; (salbutamol) 18559-94-9; (formoterol) 73573-87-2

CHEMICAL NAME: **Rezulin**; Propulsid

L148 ANSWER 48 OF 56 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001011622 EMBASE

TITLE: Plasma membrane content of glucose transporter 4 in skeletal muscle and visceral fat in OLETF rats treated with **troglitazone.**

AUTHOR: Liu Y.; Zhang J.; Xu Z.; Li X.; Zhao D.; Cui X.; Bai W.; Wang T.; Yang J.; Iwamoto Y.; Tsushima T.

CORPORATE SOURCE: Y. Liu, Department of Endocrinology, 306th Hospital, Beijing 100101, China. liuyanjun@public.gb.com.cn

SOURCE: Journal of Health Science, (2000) Vol. 46, No. 6, pp. 441-446. .
Refs: 15
ISSN: 1344-9702 CODEN: JHSCFD

COUNTRY: Japan

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 003 Endocrinology
006 Internal Medicine
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20010119
Last Updated on STN: 20010119

ABSTRACT: The exact mechanism by which **troglitazone** improves insulin sensitivity is not well understood. Eight 35-week-old male diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats were treated with **troglitazone** (30 mg/kg body weight/d) for 20 d (OLETF-T). Body composition, glucose tolerance, serum lipid profile and expression of glucose transporter 4 (Glut 4) in OLETF-T were compared with those in 8 male control OLETF rats and in 18 normal Long Evans Tokushima Otsuka (LETO) rats. Body weight, visceral fat weight, and pancreas weight in OLETF-T rats were significantly lower than those in OLETF rats ($p < 0.05$). Furthermore, **troglitazone** treatment attenuated atrophy and fibrosis of the pancreas. Serum concentrations of glucose, triglyceride, total cholesterol and immunoreactive insulin (IRI) were also significantly lower in OLETF-T rats. Expression of Glut 4 in plasma membrane fractions of skeletal muscle and visceral fat was detected by Western blot. The amount of Glut 4 protein in skeletal muscle in OLETF rats was 52% of that in LETO rats, and 75% for OLETF-T rats. In visceral fat, Glut 4 expressions in OLETF and OLETF-T rats were 38% and 83%, respectively, of that in LETO rats. Thus, treatment with **troglitazone** prevented the decrease of Glut 4 expression seen in OLETF rats. Glucose tolerance was improved significantly by the treatment, and the amount of secreted IRI in response to oral glucose tolerance test was 1798 pM, 702.2 pM, and 1103.5 pM, in OLETF, OLETF-T and LETO rats, respectively. The data presented suggest that treatment with **troglitazone** increased the Glut 4 expression in both skeletal and visceral fat tissues of OLETF rats, which may result in the improvement of insulin sensitivity and preservation of pancreas function.

CONTROLLED TERM: Medical Descriptors:
*diabetes mellitus: DT, drug therapy
*protein localization
*body fat

*skeletal muscle
cell membrane
rat strain
body composition
glucose tolerance test
lipid blood level
protein expression
body weight
cystic fibrosis
atrophy
pancreas
Western blotting
treatment outcome
insulin sensitivity
pancreas function
nonhuman
male
rat
animal experiment
animal model
controlled study
article
Drug Descriptors:
*glucose transporter: EC, endogenous compound
*glucose transporter 4: EC, endogenous compound
***troglitazone: DT, drug therapy**
***troglitazone: PD, pharmacology**
glucose: EC, endogenous compound
triacylglycerol: EC, endogenous compound
cholesterol: EC, endogenous compound
immunoreactive insulin: EC, endogenous compound
unclassified drug
CAS REGISTRY NO.: (**troglitazone**) **97322-87-7**; (glucose) 50-99-7, 84778-64-3; (cholesterol) 57-88-5

L148 ANSWER 49 OF 56 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2001186387 EMBASE
TITLE: From gene-specific tests to pharmacogenetics.
AUTHOR: Middleton L.; Freeman A.; Brewster S.; Foster C.; Roses A.
CORPORATE SOURCE: Dr. L. Middleton, GlaxoSmithKline Res. and Development, 891-995 Greenford Road, Greenford UB6 0HE, United Kingdom. LTM81817@glaxowellcome.co.uk
SOURCE: Community Genetics, (2000) Vol. 3, No. 4, pp. 198-203. .
Refs: 26
ISSN: 1422-2795 CODEN: COGEFX
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 006 Internal Medicine
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20010614
Last Updated on STN: 20010614
ABSTRACT: Over the next 3-5 years pharmacogenetics will provide opportunities to enhance the efficacy and tolerability of medicines, accelerated by the ongoing rapid development of a high-density map of single-nucleotide

polymorphisms (SNP) and of high-throughput SNP scoring technologies. It is important that this application of genetic technology is clearly differentiated from genetic tests for monogenic and complex diseases, which are associated with a number of ethical, legal and social implications. The ethical, legal and social issues associated with pharmacogenetics need to be identified and clearly differentiated from those associated with gene-specific tests for disease. Copyright .COPYRGT. 2001 S. Karger AG, Basel.

CONTROLLED TERM: Medical Descriptors:
*pharmacogenetics
*genetic disorder: DI, diagnosis
*genetic disorder: ET, etiology
*single nucleotide polymorphism
Huntington chorea: DI, diagnosis
Huntington chorea: ET, etiology
cystic fibrosis: DI, diagnosis
cystic fibrosis: ET, etiology
gene mutation
genetic counseling
drug metabolism
drug safety
drug induced disease: SI, side effect
bone marrow suppression: SI, side effect
neurotoxicity: SI, side effect
DNA sequence
enzyme deficiency
bleeding: SI, side effect
asthma: DT, drug therapy
glioma: DT, drug therapy
tuberculosis: DT, drug therapy
hyperlipidemia: DT, drug therapy
human
clinical trial
conference paper
priority journal
Drug Descriptors:
*cytochrome P450
*antineoplastic agent: AE, adverse drug reaction
*antineoplastic agent: PK, pharmacokinetics
*fluorouracil: AE, adverse drug reaction
*fluorouracil: PK, pharmacokinetics
*mercaptopurine: AE, adverse drug reaction
*mercaptopurine: PK, pharmacokinetics
*fluoxetine: AE, adverse drug reaction
*fluoxetine: PK, pharmacokinetics
*moclobemide: AE, adverse drug reaction
*moclobemide: PK, pharmacokinetics
*omeprazole: AE, adverse drug reaction
*omeprazole: PK, pharmacokinetics
cytochrome P450 2D6
cytochrome P450 2C9
cytochrome P450 2C19
warfarin: AE, adverse drug reaction
warfarin: PK, pharmacokinetics
phenytoin: AE, adverse drug reaction
phenytoin: PK, pharmacokinetics
tolbutamide: AE, adverse drug reaction
tolbutamide: PK, pharmacokinetics
glipizide: AE, adverse drug reaction
glipizide: PK, pharmacokinetics

nifedipine: AE, adverse drug reaction
nifedipine: PK, pharmacokinetics
antiarrhythmic agent: AE, adverse drug reaction
antiarrhythmic agent: PK, pharmacokinetics
antidepressant agent: AE, adverse drug reaction
antidepressant agent: PK, pharmacokinetics
opiate: AE, adverse drug reaction
opiate: PK, pharmacokinetics
formoterol: CT, clinical trial
formoterol: AD, drug administration
formoterol: DT, drug therapy
formoterol: PD, pharmacology
formoterol: IH, inhalational drug administration
beta 2 adrenergic receptor stimulating agent: CT, clinical trial
beta 2 adrenergic receptor stimulating agent: AD, drug administration
beta 2 adrenergic receptor stimulating agent: DT, drug therapy
beta 2 adrenergic receptor stimulating agent: PD, pharmacology
beta 2 adrenergic receptor stimulating agent: IH, inhalational drug administration
isoniazid: AE, adverse drug reaction
isoniazid: DT, drug therapy
isoniazid: PK, pharmacokinetics
tuberculostatic agent: AE, adverse drug reaction
tuberculostatic agent: DT, drug therapy
tuberculostatic agent: PK, pharmacokinetics
pravastatin: DT, drug therapy
pravastatin: PD, pharmacology
hydroxymethylglutaryl coenzyme A reductase inhibitor: DT, drug therapy
hydroxymethylglutaryl coenzyme A reductase inhibitor: PD, pharmacology
antilipemic agent: DT, drug therapy
antilipemic agent: PD, pharmacology
benoxaprofen: AE, adverse drug reaction
terfenadine: AE, adverse drug reaction
troglitazone: AE, adverse drug reaction
carmustine: DT, drug therapy
carmustine: PD, pharmacology
unindexed drug

CAS REGISTRY NO.: (cytochrome P450) 9035-51-2; (fluorouracil) 51-21-8; (mercaptopurine) 31441-78-8, 50-44-2, 6112-76-1; (fluoxetine) 54910-89-3, 56296-78-7, 59333-67-4; (moclobemide) 71320-77-9; (omeprazole) 73590-58-6, 95510-70-6; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2; (phenytoin) 57-41-0, 630-93-3; (tolbutamide) 473-41-6, 64-77-7; (glipizide) 29094-61-9; (nifedipine) 21829-25-4; (opiate) 53663-61-9, 8002-76-4, 8008-60-4; (formoterol) 73573-87-2; (isoniazid) 54-85-3, 62229-51-0, 65979-32-0; (pravastatin) 81131-74-0; (benoxaprofen) 51234-28-7; (terfenadine) 50679-08-8; (**troglitazone**) **97322-87-7**; (carmustine) 154-93-8

L148 ANSWER 50 OF 56 EMBASE
ACCESSION NUMBER: 2000219418 EMBASE

TITLE: Correction of hyperinsulinemia in oligoovulatory women with clomiphene- resistant polycystic ovary syndrome: A review of therapeutic rationale and reproductive outcomes.

AUTHOR: Sills E.S.; Perloe M.; Palermo G.D.
CORPORATE SOURCE: Dr. E.S. Sills, 5445 Meridian Mark Rd., Atlanta, GA 30342, United States. dr.sills@ivf.com

SOURCE: European Journal of Obstetrics Gynecology and Reproductive Biology, (2000) Vol. 91, No. 2, pp. 135-141. .
Refs: 33
ISSN: 0301-2115 CODEN: EOGRAL
PUBLISHER IDENT.: S 0301-2115(99)00287-0
COUNTRY: Ireland
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
010 Obstetrics and Gynecology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20000720
Last Updated on STN: 20000720

ABSTRACT: Polycystic ovary syndrome (PCOS) describes a convergence of chronic multisystem endocrine derangements, including irregular menses, hirsutism, obesity, hyperlipidemia, androgenization, large and **cystic**-appearing ovaries, insulin resistance and subfertility. Few PCOS patients exhibit all of these features, and often only one sign or symptom is evident. The sequelae of PCOS reach beyond reproductive health, as women affected with PCOS have increased relative risks for myocardial infarction, hypertension, ischemic heart disease, thromboembolic disease and diabetes. Although the adverse health consequences associated with PCOS are substantial, unfortunately most women are not aware of these risks. Indeed, in infertility practice such concerns are secondary as most patients are referred for treatment specifically to achieve a pregnancy. Impairments in insulin metabolism appear central to the physiologic cascade of PCOS, yet clomiphene therapy fails to remedy this defect. Several investigators have described satisfactory reproductive outcomes for PCOS patients treated with oral insulin-lowering agents. In this report, we outline a diagnostic and therapeutic approach for women with PCOS refractory to clomiphene with attention to the underlying insulin imbalance associated with impaired fertility. (C) 2000 Elsevier Science Ireland Ltd.

CONTROLLED TERM: Medical Descriptors:
*hyperinsulinemia: CO, complication
*hyperinsulinemia: DT, drug therapy
*hyperinsulinemia: ET, etiology
*ovary polycystic disease: DI, diagnosis
*ovary polycystic disease: DR, drug resistance
*ovary polycystic disease: DT, drug therapy
*hormonal therapy
clinical feature
heart infarction: CO, complication
hypertension: CO, complication
ischemic heart disease: CO, complication
thromboembolism: CO, complication
diabetes mellitus: CO, complication
insulin metabolism
treatment outcome
drug efficacy
menstrual cycle
dose response

dexamethasone suppression test
lactic acidosis: SI, side effect
female fertility
ovulation
human
clinical trial
review
priority journal
Drug Descriptors:
*clomifene: CB, drug combination
*clomifene: DT, drug therapy
*clomifene: PD, pharmacology
*insulin: EC, endogenous compound
*metformin: AE, adverse drug reaction
*metformin: DO, drug dose
*metformin: DT, drug therapy
*metformin: PD, pharmacology
*metformin: PO, oral drug administration
dexamethasone: DT, drug therapy
alanine aminotransferase: EC, endogenous compound
rosiglitazone: CB, drug combination
rosiglitazone: DT, drug therapy
piaglitazone: CB, drug combination
piaglitazone: DT, drug therapy
oral antidiabetic agent: AE, adverse drug reaction
oral antidiabetic agent: DO, drug dose
oral antidiabetic agent: DT, drug therapy
oral antidiabetic agent: PD, pharmacology
unclassified drug

CAS REGISTRY NO.: (clomifene) 911-45-5; (insulin) 9004-10-8; (metformin) 1115-70-4, 657-24-9; (dexamethasone) 50-02-2; (alanine aminotransferase) 9000-86-6, 9014-30-6; (**rosiglitazone**) **122320-73-4**, **155141-29-0**

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ACCESSION NUMBER: 2000199718 EMBASE
TITLE: 29th Annual Meeting of New England Pharmacologists Brown University, Providence, RI January 28-29, 2000.
AUTHOR: Scriabine A.
CORPORATE SOURCE: Dr. A. Scriabine, Department of Pharmacology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06420, United States. alexander.scriabine@snet.net
SOURCE: Cardiovascular Drug Reviews, (2000) Vol. 18, No. 1, pp. 89-92. .
ISSN: 0897-5957 CODEN: CDREEA
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 008 Neurology and Neurosurgery
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 20000630
Last Updated on STN: 20000630
CONTROLLED TERM: Medical Descriptors:
*cardiovascular disease: ET, etiology
*cardiovascular disease: PC, prevention

*neurologic disease: DT, drug therapy
*neurologic disease: ET, etiology
*neurologic disease: PC, prevention
*amyotrophic lateral sclerosis: DT, drug therapy
atherosclerosis: ET, etiology
atherosclerosis: PC, prevention
gene mutation
neuropharmacology
drug mechanism
brain protection
withdrawal syndrome
cystic fibrosis: ET, etiology
non insulin dependent diabetes mellitus: DT, drug therapy
drug induced disease: SI, side effect
nausea: SI, side effect
vomiting: SI, side effect
coughing: SI, side effect
human
nonhuman
conference paper
priority journal
Drug Descriptors:
*recombinant ciliary neurotrophic factor: AE, adverse drug reaction
*recombinant ciliary neurotrophic factor: DT, drug therapy
*recombinant ciliary neurotrophic factor: PD, pharmacology
*leptin
*cholinergic receptor
cholesterol ester transfer protein
epitope
tetanus toxoid: DV, drug development
4 aminobutyric acid A receptor
benzodiazepine receptor blocking agent
flumazenil
serotonin 1B receptor
eletriptan: CM, drug comparison
eletriptan: PK, pharmacokinetics
zolmitriptan: CM, drug comparison
zolmitriptan: PK, pharmacokinetics
sumatriptan: CM, drug comparison
sumatriptan: PK, pharmacokinetics
4 aminobutyric acid B receptor stimulating agent: DO, drug dose
4 aminobutyric acid B receptor stimulating agent: IP, intraperitoneal drug administration
baclofen: DO, drug dose
baclofen: CE, intracerebral drug administration
baclofen: IP, intraperitoneal drug administration
cannabinoid receptor antagonist
dronabinol
5 (4 chlorophenyl) 1 (2,4 dichlorophenyl) 4 methyl n (1 piperidyl) 1h pyrazole 3 carboxamide
rosiglitazone
lidocaine
neurosteroid
mevinolin
morphine: DO, drug dose
morphine: SC, subcutaneous drug administration
verapamil
nifedipine

diltiazem
lidocaine ethobromide
CAS REGISTRY NO.: (tetanus toxoid) 57425-69-1, 93384-51-1; (flumazenil) 78755-81-4; (eletriptan) 143322-58-1; (zolmitriptan) 139264-17-8; (sumatriptan) 103628-46-2; (baclofen) 1134-47-0; (dronabinol) 7663-50-5; (5 (4 chlorophenyl) 1 (2,4 dichlorophenyl) 4 methyl n (1 piperidyl) 1h pyrazole 3 carboxamide) 158681-13-1; (**rosiglitazone**) **122320-73-4, 155141-29-0**; (lidocaine) 137-58-6, 24847-67-4, 56934-02-2, 73-78-9; (mevinolin) 75330-75-5; (morphine) 52-26-6, 57-27-2; (verapamil) 152-11-4, 52-53-9; (nifedipine) 21829-25-4; (diltiazem) 33286-22-5, 42399-41-7; (lidocaine ethobromide) 21306-56-9
CHEMICAL NAME: Qx 314; Sr 141716a

L148 ANSWER 52 OF 56 EMBASE
ACCESSION NUMBER: 1999436563 EMBASE
TITLE: Diabetes mellitus in **cystic** fibrosis.
AUTHOR: Hardin D.S.; Moran A.
CORPORATE SOURCE: Dr. A. Moran, University of Minnesota, Department of Pediatrics, Phillips Wangensteen Building, 13-128 516 Delaware Street, Minneapolis, MN 55455, United States. moran001@tc.umn.edu
SOURCE: Endocrinology and Metabolism Clinics of North America, (1999) Vol. 28, No. 4, pp. 787-800. .
Refs: 54
ISSN: 0889-8529 CODEN: ECNAER
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
007 Pediatrics and Pediatric Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20000107
Last Updated on STN: 20000107
ABSTRACT: Glucose intolerance and diabetes are common complications of ***cystic*** fibrosis (CF), affecting up to 75% of the adult population. This article discusses the prevalence and pathophysiology of glucose tolerance abnormalities in CF, and reviews recent recommendations for diagnosis, screening, and management of CF-related diabetes (CFRD).

CONTROLLED TERM: Medical Descriptors:
*diabetes mellitus: CO, complication
*diabetes mellitus: DI, diagnosis
*diabetes mellitus: DT, drug therapy
***cystic fibrosis**
glucose intolerance: CO, complication
impaired glucose tolerance: DI, diagnosis
impaired glucose tolerance: ET, etiology
pathophysiology
prevalence
disease association
insulin dependent diabetes mellitus
non insulin dependent diabetes mellitus
diet restriction
human
review
priority journal

Drug Descriptors:
*insulin: DT, drug therapy
*sulfonylurea derivative: DT, drug therapy
troglitazone: DT, drug therapy
glibenclamide: DT, drug therapy
metformin: DT, drug therapy
CAS REGISTRY NO.: (insulin) 9004-10-8; (**troglitazone**) **97322-87-7**; (glibenclamide) 10238-21-8; (metformin) 1115-70-4, 657-24-9

L148 ANSWER 53 OF 56 EMBASE
ACCESSION NUMBER: 1998272614 EMBASE
TITLE: The diagnosis and management of **cystic** fibrosis related diabetes.
AUTHOR: Hardin D.S.
CORPORATE SOURCE: Dr. D.S. Hardin, Baylor College of Medicine, M.S.B. 3.122, 6431 Fannin, Houston, TX 77030, United States. dhardin@pedl.med.uth.edu
SOURCE: Endocrinologist, (1998) Vol. 8, No. 4, pp. 265-272. .
Refs: 22
ISSN: 1051-2144 CODEN: EDOCEB
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19980917
Last Updated on STN: 19980917

ABSTRACT: The incidence of abnormal glucose tolerance and diabetes mellitus in patients with **cystic** fibrosis (CF) is higher than in any other age-matched group. Diabetes in CF patients shares some clinical features with both type 1 and type 2 diabetes, but it is a unique disease and is called ***cystic*** fibrosis related diabetes (CFRD). Causes of CFRD include decreased insulin secretion, secondary to pancreatic insufficiency, and impaired insulin action. Patients with CFRD have increased morbidity and mortality and are subject to the same microvascular complications as non-CF patients. The goal of this article is to provide better understanding of the etiology and clinical consequences of CFRD and to provide endocrinologists with specific recommendations for diagnosis and management.

CONTROLLED TERM: Medical Descriptors:
***cystic fibrosis**
*diabetes mellitus: CO, complication
*diabetes mellitus: DI, diagnosis
*diabetes mellitus: DT, drug therapy
impaired glucose tolerance
insulin release
pancreas insufficiency
insulin resistance
dietary intake
diabetic retinopathy: CO, complication
diabetic neuropathy: CO, complication
glucose blood level
hemoglobin analysis
disease classification
dose time effect relation
human

oral drug administration
article
Drug Descriptors:
*insulin: AD, drug administration
*insulin: DO, drug dose
*insulin: DT, drug therapy
*human insulin: AD, drug administration
*human insulin: DO, drug dose
*human insulin: DT, drug therapy
*insulin[b28 lysine b29 proline]: AD, drug administration
*insulin[b28 lysine b29 proline]: DO, drug dose
*insulin[b28 lysine b29 proline]: DT, drug therapy
*isophane insulin: AD, drug administration
*isophane insulin: DO, drug dose
*isophane insulin: DT, drug therapy
*insulin zinc suspension: AD, drug administration
*insulin zinc suspension: DO, drug dose
*insulin zinc suspension: DT, drug therapy
glipizide: DT, drug therapy
glibenclamide: DT, drug therapy
metformin: DT, drug therapy
troglitazone: DT, drug therapy
hemoglobin a1c: EC, endogenous compound
CAS REGISTRY NO.: (insulin) 9004-10-8; (human insulin) 11061-68-0; (insulin[b28 lysine b29 proline]) 133107-64-9; (isophane insulin) 9004-17-5; (insulin zinc suspension) 8049-62-5; (glipizide) 29094-61-9; (glibenclamide) 10238-21-8; (metformin) 1115-70-4, 657-24-9; (**troglitazone**) **97322-87-7**; (hemoglobin a1c) 62572-11-6

L148 ANSWER 54 OF 56 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:295244 BIOSIS
DOCUMENT NUMBER: PREV200300295244
TITLE: Prevention of cholera and E. coli toxin-induced intestinal ion and fluid secretion by a small molecule **CFTR** inhibitor.
AUTHOR(S): Thiagarajah, Jay R. [Reprint Author]; Broadbent, Talmage; Verkman, Alan S.
CORPORATE SOURCE: Medicine and Physiology, Cardiovascular Research Institute, U.C.S.F, 1246 HSE, 505 Parnassus Avenue, San Francisco, CA, 94143-0521, USA
jayt@itsa.ucsf.edu; tb59@email.byu.edu; verkman@itsa.ucsf.edu
SOURCE: FASEB Journal, (March 2003) Vol. 17, No. 4-5, pp. Abstract No. 600.14. http://www.fasebj.org/. e-file.
Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. San Diego, CA, USA. April 11-15, 2003. FASEB.
ISSN: 0892-6638 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Jun 2003
Last Updated on STN: 25 Jun 2003
ABSTRACT:Secretory diarrhea is the leading cause of infant death in developing countries and a major cause of morbidity in adults with >5 million deaths annually. The bacterial enterotoxins cholera toxin (CT) and heat stable enterotoxin (STa) from E. coli are major agents causing secretory diarrhea by inducing chloride and hence fluid secretion into the intestine. The

cystic fibrosis transmembrane conductance regulator (**CFTR**) protein provides the apical route for chloride secretion across intestinal epithelia. We recently identified a thiazolidinone-type **CFTR** blocker (3-[(3-trifluoromethyl)phenyl]-5-[(3-carboxyphenyl) methylene]-2-***thioxo*** -4-**thiazolidinone**, **CFTRinh**-172) by high-throughput screening (J. Clin. Invest. in press, Dec. 2002). In T84 colonic epithelial cells **CFTRinh**-172 inhibited cAMP and cGMP-induced short-circuit current with KI apprx 5 ?M, but did not inhibit calcium-induced currents. In mice, a single intraperitoneal injection of **CFTRinh**-172 (20 mug) inhibited cholera toxin-induced intestinal fluid accumulation by 90% (t1/2 apprx3 h) with 50% inhibition at 4 mug. In rats, 200 mug **CFTRinh** -172 blocked intestinal fluid secretion by > 80% for cholera toxin and by > 70% for STa E. coli toxin. **CFTRinh**-172 blocked transepithelial short-circuit current in colonic sheets in response to cAMP and cGMP agonists. These findings show marked reduction by a **CFTR** blocker in intestinal ion and fluid secretion caused by cAMP/cGMP-dependent bacterial enterotoxins. ***CFTR*** inhibition may thus reduce fluid secretion in infectious secretory diarrheas.

CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Biochemistry studies - General 10060
Biophysics - Membrane phenomena 10508
Digestive system - Physiology and biochemistry 14004
Digestive system - Pathology 14006
Morphology and cytology of bacteria 30500
Physiology and biochemistry of bacteria 31000
Medical and clinical microbiology - Bacteriology 36002

INDEX TERMS: Major Concepts
Digestive System (Ingestion and Assimilation); Infection; Membranes (Cell Biology)

INDEX TERMS: Diseases
bacterial secretory diarrhea: bacterial disease, digestive system disease

INDEX TERMS: Diseases
cholera: bacterial disease, digestive system disease
Cholera (MeSH)

INDEX TERMS: Chemicals & Biochemicals
chloride: secretion; cholera toxin; **cystic** fibrosis transmembrane conductance regulator [**CFTR**]

ORGANISM: Classifier
Enterobacteriaceae 06702
Super Taxa
Facultatively Anaerobic Gram-Negative Rods; Eubacteria; Bacteria; Microorganisms
Organism Name
E. coli (miscellaneous) [Escherichia coli (species)]: pathogen
Taxa Notes
Bacteria, Eubacteria, Microorganisms

ORGANISM: Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse (common)
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

REGISTRY NUMBER: 16887-00-6 (chloride)

L148 ANSWER 55 OF 56 USPATFULL on STN
ACCESSION NUMBER: 2005:318869 USPATFULL
TITLE: Methods, compositions and compound assays for inhibiting amyloid-beta protein production
INVENTOR(S): Merchiers, Pascal Gerard, Tielen, BELGIUM
Spittaels, Koenraad Frederik Florentina, Puurs, BELGIUM

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005277612	A1	20051215
APPLICATION INFO.:	US 2005-110011	A1	20050420 (11)

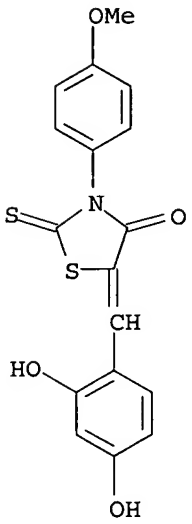
	NUMBER	DATE
PRIORITY INFORMATION:	US 2004-563764P	20040420 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SYNNESTVEDT & LECHNER, LLP, 2600 ARAMARK TOWER, 1101 MARKET STREET, PHILADELPHIA, PA, 191072950, US
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Page(s)
LINE COUNT: 2187
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for identifying compounds that inhibit amyloid-beta precursor protein processing in cells, comprising contacting a test compound with a SPHK polypeptide, or fragment thereof, and measuring a compound-SPHK property related to the production of amyloid-beta peptide. Cellular assays of the method measure indicators including phosphorylated kinase substrate and/or amyloid beta peptide levels. Therapeutic methods, and pharmaceutical compositions including effective amyloid-beta precursor processing-inhibiting amounts of SPHK expression inhibitors, are useful for treating conditions involving cognitive impairment such as Alzheimer's Disease.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . and structural formulae below, are disclosed in these references, which are incorporated by reference,

A: Compounds 306301-68-8, 312636-16-1, **359899-55-1** and 24388-08-7 (French et al., 2003)
B: DMS (N-dimethylsphingosine, D-erythro (BIOMOL)).
C: S15183A (3. 7-octanoyloxy-3-heptyl-7-methyl-6,8-dioxo-2-oxa-2,6,7,8-tetrahydronaphthalene)
D: F-12509. . .
DETD . . . promoters (e.g. HPRT, vimentin, actin, tubulin), intermediate filament promoters (e.g. desmin, neurofilaments, keratin, GFAP), therapeutic gene promoters (e.g. MDR type, **CFTR**, factor VIII), tissue-specific promoters (e.g. actin promoter in smooth muscle cells, or Flt and Flk promoters active in endothelial cells),. . .
IT 24388-08-7 119567-63-4, N,N-Dimethylsphingosine 191608-64-7 210905-11-6, S 15183 A 306301-68-8 312636-16-1 **359899-55-1**
(SPHK inhibitor; methods, compns. and compound assays for inhibiting β-amyloid protein production by inhibiting sphingosine kinase (SPHK), and anti-Alzheimer's uses)

IT **359899-55-1**
(SPHK inhibitor; methods, compns. and compound assays for inhibiting β-amyloid protein production by inhibiting sphingosine kinase (SPHK), and anti-Alzheimer's uses)
RN 359899-55-1 USPATFULL
CN 4-Thiazolidinone, 5-[(2,4-dihydroxyphenyl)methylene]-3-(4-methoxyphenyl)-2-thioxo- (9CI) (CA INDEX NAME)



L148 ANSWER 56 OF 56 USPATFULL on STN
ACCESSION NUMBER: 2004:178306 USPATFULL
TITLE: Methods and compositions for modification of splicing of pre-mRNA
INVENTOR(S): Kole, Ryszard, Chapel Hill, NC, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004137472	A1	20040715
APPLICATION INFO.:	US 2003-672501	A1	20030926 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-414141P	20020927 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MYERS BIGEL SIBLEY & SAJOVEC, PO BOX 37428, RALEIGH, NC, 27627
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Page(s)
LINE COUNT: 908
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides a method of preventing a splicing event in a pre-mRNA molecule, comprising contacting the pre-mRNA and/or elements of the splicing machinery with a small molecule compound identified according to the methods described herein to prevent the splicing event in the pre-mRNA molecule. Further provided is a method of inducing a splicing event in a pre-mRNA molecule, comprising contacting

the pre-mRNA and/or elements of the splicing machinery with a small molecule compound identified according to the methods described herein to induce the splicing event in the pre-mRNA molecule. Furthermore, a method is provided herein of treating a patient having a disorder associated with an alternative or aberrant splicing event in a pre-mRNA molecule, comprising administering to the patient a therapeutically effective amount of a compound identified according to the methods described herein to prevent an alternative or aberrant splicing event in a pre-mRNA molecule, thereby treating the patient.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . would bind to β-hexoseaminidase α-subunit pre-mRNA), phenylketonuria (wherein the oligonucleotide would bind to phenylalanine hydroxylase pre-mRNA) and certain forms of **cystic fibrosis** (wherein the oligonucleotide would bind the **cystic fibrosis** gene pre-mRNA), in which mutations leading to aberrant splicing of pre-mRNA have been identified (See, e.g., S. Akli et al.,. . .

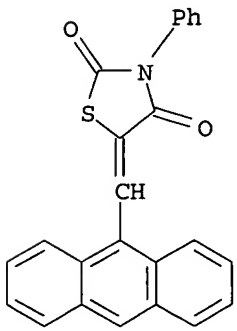
DETD . . . as topical administration (e.g., administration of an aerosolized formulation of respirable particles to the lungs of a patient afflicted with **cystic fibrosis** or lung cancer or a cream or lotion formulation for transdermal administration of patients with psoriasis). The formulations may conveniently. . .

IT 56813-52-6 60792-56-5, 1H-Benzimidazole-2-acetamide 123299-47-8
211565-51-4 **292172-90-8** 299418-26-1 312526-46-8
313483-60-2 316132-86-2 324774-89-2 325970-31-8 327030-83-1
332897-12-8 353472-06-7 353782-10-2 360050-83-5 393134-41-3
413617-61-5 414882-19-2 414886-90-1 414892-23-2 415694-94-9
415921-88-9 415953-80-9 415954-13-1 415960-24-6 416870-10-5
416872-75-8 416886-08-3 416892-46-1 416896-09-8 418776-59-7
418788-50-8 419539-02-9 465536-61-2 467449-15-6 676515-94-9
(small organic mols. for modification of splicing of pre-mRNA, screening method, and therapeutic use)

IT **292172-90-8**
(small organic mols. for modification of splicing of pre-mRNA, screening method, and therapeutic use)

RN 292172-90-8 USPATFULL

CN 2,4-Thiazolidinedione, 5-(9-anthracenylmethylene)-3-phenyl- (9CI) (CA INDEX NAME)



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